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ORIGINAL ARTICLES

MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY OF MALE CHILDREN AND ADOLESCENTS

By B. G. FERRIS, JR., M.D., J. L. WHITTENBERGER, M.D., AND J. R. GALLAGHER, M.D.

Boston

ATTEMPTS to study the pulmonary function of children and adolescents having residual effects from poliomyelitis have made apparent the need for adequate standards of the maximum breathing capacity of normal individuals of these age groups. Existing reports concerning normal values for the vital capacity in children[1-3] and the standards for the maximum breathing capacity and vital capacity in adults[4,5] do not fill this need. The adult standards of vital capacity are based on age and height and those for the maximum breathing capacity upon age and surface area. Both tend to give too high values for children and too low values for adolescents. Furthermore, the standards of Baldwin et al.[4] are based on a hospital population. Although their subjects had no demonstrable pulmonary or cardiac disease, all had been hospitalized and, therefore, presumably had been inactive for varying periods. Since physical inactivity results in a significant diminution of muscular power, an important factor in the maximum breathing capacity, it is possible that the results of Baldwin et al. may have been influenced by that factor. The standards of Gray et al.[5] are based on a healthy young adult population and for that reason are not applicable to children.

In an effort to obtain standards for the maximum breathing capacity of the younger age group, a group of boys at Phillips Academy, Andover, and the Rivers Country Day School, Brookline, were studied. The vital capacity of the subjects was also measured so that it could be used as an index of comparison with the results of other investigators.

METHODS

The subjects were healthy, active boys whose ages varied from 5 to 18 yr. A total of 161 boys were studied. Vital capacities and maximum breathing capacities were measured in a Benedict-Roth

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type spirometer (Collins Ventilometer) with the soda lime container and valves removed. The vital capacity used was the largest of 3 or more maximal expirations following a maximal inspiration. The younger children were encouraged to "blow out all the candles on your birthday cake." The indication for more than 3 measurements was a progressive rise in the values obtained. Similarly, the greatest of 3 determinations of the maximum breathing capacity were used; if there was a progressive increase, further determinations were made. Since the training factor in the maximum breathing capacity is considerable, more than 3 runs were often necessary. Intervals of 1 to 2 min. were allowed between these determinations for rest, since, when done properly, the maximum breathing capacity is strenuous exercise. These determinations were done by having the subject breathe as deeply and as rapidly as possible, but allowing him to select his own depth and rate. A 15 sec. period was used after the first few breaths to permit him to reach his maximal effort. The values so obtained were extrapolated to 1 min. periods. All measurements were done with the subject seated, but free movement of the arms and shoulders was possible.

The resistance developed in the spirometer system was determined at a mean air-flow rate of 350 l./min. This simulated conditions of a voluntary breathing capacity at a level of 175 l./min. The instantaneous peak flow rate under these conditions was about 500 l./min., and the resistance of the system was 14 cm. water at this peak flow velocity. Values of the same order of magnitude were obtained on inspiration and expiration; however, the precise timing of the peak resistance in the cycle of respiration was not possible. This resistance is composed of several elements: (1) the resistance of the tubing (2 tubes with 1.9 cm. inside diameter) and the mouthpiece, (2) the inertia of the bell and the oscillations in the water seal and (3) the frictional resistance of the mechanical recording apparatus. The contributions of these various elements to the total resistance have not been determined, but it can be predicted that the component due to inertia would be greatest at the time of maximum acceleration and that the one due to the resistance of the tubing would be greatest at the highest flow rates.

All ventilatory values were corrected to body temperature and ambient pressure conditions and saturated with water vapor at 37° C. (BTPS).* The maximum breathing capacity was recorded to the nearest l./min. and the vital capacity to the nearest 0.01 l.

The subjects were weighed to the nearest 0.5 kg. without heavy clothing (shoes and coats), and their heights in stocking feet were recorded to the nearest centimeter. The body surface area was obtained from a Dubois nomogram. This was read to the nearest 0.01 M^2. Birth dates were recorded, and the age at the time of the ventilatory measurements was calculated to the nearest month. All measurements were made by the same observer.

Results

The results are presented in tables 1 to 8 where the average vital capacities and maximum breathing capacities for the various groupings are shown. The individual results have been plotted as scattergrams (charts 1-8) against the different physical characteristics (age, height, weight, and body surface area). Smoothed curves for the mean values (solid line) and the two standard deviation ranges (dashed lines) above and below the means have been constructed and plotted on the scattergrams.

It is interesting to note the change of slope that occurs in the voluntary breathing capacity values and the vital capacity values when they are plotted against age. The age (12 to 14 years) at which this occurs is a period of rapid growth in boys and a time when there is a pronounced increase in chest size and muscle mass. Because of these develop-

* Volume corrected = volume observed $\times \frac{310}{\text{Observed temp. °C} + 273°} \times \frac{\text{Observed bar. pressure} - \text{Vapor tension of water at observed temperature}}{\text{Observed bar. pressure} - 47 \text{ (Vapor tension of water at 37° C)}}$

TABLE 1

VITAL CAPACITY IN LITERS IN RELATION TO AGE IN YEARS

Age (yr.)	5.0 to 5.9	6.0 to 6.9	7.0 to 7.9	8.0 to 8.9	9.0 to 9.9	10.0 to 10.9	11.0 to 11.9	12.0 to 12.9	13.0 to 13.9	14.0 to 14.9	15.0 to 15.9	16.0 to 16.9	17.0 to 17.9
No.	4	8	6	7	7	10	6	3	20	72	9	5	4
Mean L.	1.29	1.65	1.93	2.16	2.17	2.23	2.54	3.75	3.81	4.29	4.47	4.51	4.49
Std. dev. L.	0.23	0.19	0.24	0.41	0.24	0.24	0.37	0.27	0.64	0.76	0.62	0.42	0.41

TABLE 2

MAXIMUM BREATHING CAPACITY IN LITERS/MINUTE IN RELATION TO AGE IN YEARS

Age (yr.)	5.0 to 5.9	6.0 to 6.9	7.0 to 7.9	8.0 to 8.9	9.0 to 9.9	10.0 to 10.9	11.0 to 11.9	12.0 to 12.9	13.0 to 13.9	14.0 to 14.9	15.0 to 15.9	16.0 to 16.9	17.0 to 17.9
No.	4	8	6	7	7	10	6	3	20	72	9	5	4
Mean LPM	42	45	65	69	73	79	75	109	117	117	129	134	155
Std. Dev. LPM	6	10	6	10	19	18	7	17	25	25	34	13	11

TABLE 3

VITAL CAPACITY IN LITERS IN RELATION TO WEIGHT IN KILOGRAMS

Wt. (kg.)	20.0 to 24.9	25.0 to 29.9	30.0 to 34.9	35.0 to 39.9	40.0 to 44.9	45.0 to 49.9	50.0 to 54.9	55.0 to 59.9	60.0 to 64.9	65.0 to 69.9	70.0 to 74.9	75.0 to 79.9	80.0 to 84.9
No.	9	7	12	11	10	15	8	22	29	12	12	11	3
Mean L.	1.53	1.72	2.10	2.31	2.66	3.26	3.85	4.14	4.34	4.14	4.86	4.87	4.52
Std. Dev. L.	0.32	0.22	0.20	0.43	0.37	0.53	0.47	0.53	0.71	0.66	0.46	0.75	0.28

TABLE 4

MAXIMUM BREATHING CAPACITY IN LITERS/MINUTE IN RELATION TO WEIGHT IN KILOGRAMS

Wt. (kg.)	20.0 to 24.0	25.0 to 29.9	30.0 to 34.9	35.0 to 39.9	40.0 to 44.9	45.0 to 49.9	50.0 to 54.9	55.0 to 59.9	60.0 to 64.9	65.0 to 69.9	70.0 to 74.9	75.0 to 79.9	80.0 to 84.9
No.	9	7	12	11	10	15	8	22	29	12	12	11	3
Mean LPM	46	53	74	71	83	93	110	121	129	119	126	122	136
Std. Dev. LPM	9	16	17	16	11	10	29	18	27	27	32	24	16

TABLE 5

VITAL CAPACITY IN LITERS IN RELATION TO BODY SURFACE AREA IN METERS²

B.S.A. M²	0.70 to 0.89	0.90 to 0.99	1.00 to 1.09	1.10 to 1.19	1.20 to 1.29	1.30 to 1.39	1.40 to 1.49	1.50 to 1.59	1.60 to 1.69	1.70 to 1.79	1.80 to 1.89	1.90 to 1.99	2.00 to 2.09
No.	8	5	9	9	10	10	11	12	22	36	12	14	3
Mean L.	1.52	1.63	1.99	2.10	2.47	2.57	3.36	3.53	4.08	4.32	4.85	4.88	5.39
Std. Dev. L.	0.34	0.15	0.26	0.18	0.42	0.41	0.34	0.61	0.49	0.47	0.57	0.60	0.39

TABLE 6

MAXIMUM BREATHING CAPACITY IN LITERS/MINUTE IN RELATION TO BODY SURFACE AREA IN METERS²

B.S.A. M²	0.70 to 0.89	0.90 to 0.99	1.00 to 1.09	1.10 to 1.19	1.20 to 1.29	1.30 to 1.39	1.40 to 1.49	1.50 to 1.59	1.60 to 1.69	1.70 to 1.79	1.80 to 1.89	1.90 to 1.99	2.00 to 2.09
No.	8	5	9	9	10	10	11	12	22	36	12	14	3
Mean LPM	46	48	65	70	79	84	93	108	110	130	130	125	148
Std. Dev. LPM	9	16	15	19	12	11	7	28	20	23	30	26	12

TABLE 7

VITAL CAPACITY IN LITERS IN RELATION TO HEIGHT IN CENTIMETERS

Ht. (cm.)	110.0 to 119.9	120.0 to 124.9	125.0 to 129.9	130.0 to 134.9	135.0 to 139.9	140.0 to 144.9	145.0 to 149.9	150.0 to 154.9	155.0 to 159.9	160.0 to 164.9	165.0 to 169.9	170.0 to 174.9	175.0 to 179.9	180.0 to 184.9
No.	7	5	4	5	9	9	9	5	12	13	30	29	16	8
Mean L.	1.46	1.64	1.79	2.05	2.27	2.41	2.38	2.69	3.52	3.72	4.07	4.47	4.82	5.24
Std. Dev. L.	0.32	0.16	0.18	0.21	0.45	0.41	0.31	0.45	0.44	0.47	0.45	0.55	0.54	0.49

TABLE 8

MAXIMUM BREATHING CAPACITY IN LITERS/MINUTE IN RELATION TO HEIGHT IN CENTIMETERS

Ht. (cm.)	110.0 to 119.9	120.0 to 124.9	125.0 to 129.9	130.0 to 134.9	135.0 to 139.9	140.0 to 144.9	145.0 to 149.9	150.0 to 154.9	155.0 to 159.9	160.0 to 164.9	165.0 to 169.9	170.0 to 174.9	175.0 to 179.9	180.0 to 184.9
No.	7	5	4	5	9	9	9	5	12	13	30	29	16	8
Mean LPM	44	45	63	69	68	79	82	86	102	115	113	127	129	148
Std. Dev. LPM	7	12	9	18	19	8	12	19	15	27	24	26	11	19

TABLE 9

COMPARISONS OF VITAL CAPACITY BY DIFFERENT OBSERVERS

Present Values		Robinson[3]		Wilson and Edwards[1]	
B.S.A.*	V.C.†	B.S.A.	V.C.	B.S.A.	V.C.
M^2	L.	M^2	L.	M^2	L.
0.80	1.52	0.81	1.26		
0.95	1.63				
1.05	1.99			1.05	2.00
1.15	2.10	1.12	2.20		
1.25	2.47			1.25	2.38
1.35	2.57			1.35	2.57
1.45	3.36			1.45	2.76
1.55	3.53			1.55	2.95
1.65	4.08	1.61	3.71		
1.75	4.32				
1.85	4.85	1.87	4.95		
1.95	4.88				
2.05	5.39			2.05	3.90

* Body surface area.
† Vital capacity.

TABLE 10

METHOD OF DETERMINING EXPECTED MAXIMUM BREATHING CAPACITY AND VITAL CAPACITY AND RANGE OF NORMALCY FOR AN INDIVIDUAL

	M.B.C.	2σ	V.C.	2σ
	LPM	LPM	L	L
Example 1				
Age—7 8/12 yr.	64	±20*	2.0	±0.5
Ht.—126 cm.	56	24†	1.7	0.4
Wt.—25 kg.	49	20	1.6	0.5
B.S.A.—0.93 M^2	52	26	1.7	0.7
Observed	56		1.67	
Example 2				
Age—6 8/12 yr.	53	±20†	1.7	±0.4
Ht.—119 cm.	48	14	1.5	0.6
Wt.—20 kg.	42	16	1.5	0.5
B.S.A—0.81 M^2	46	18	1.5	0.7
Observed	26		1.1	

* See chart 2 in which 2 σ is 20 LPM.
† See chart 8 in which σ is 24 LPM.

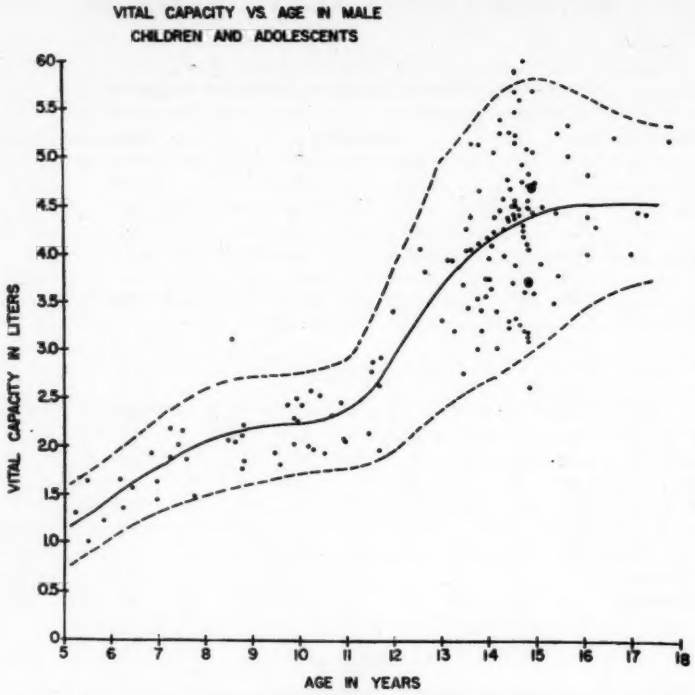
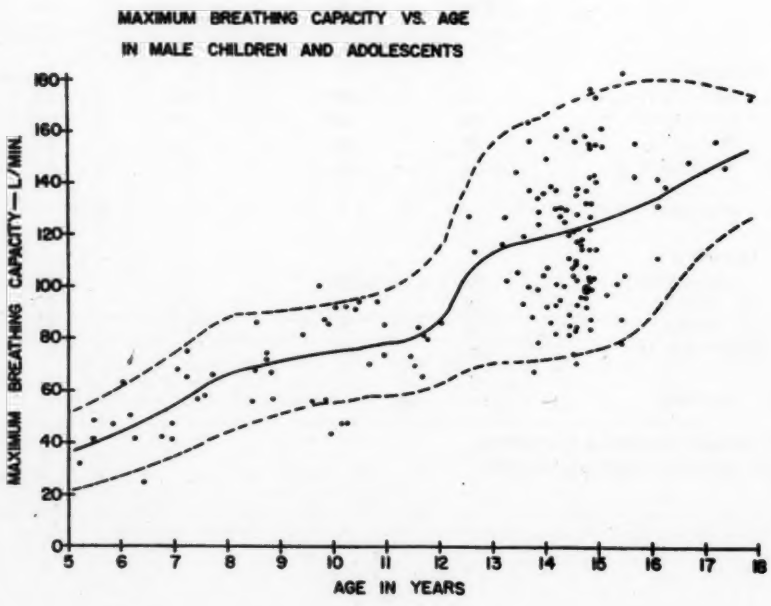


CHART 1



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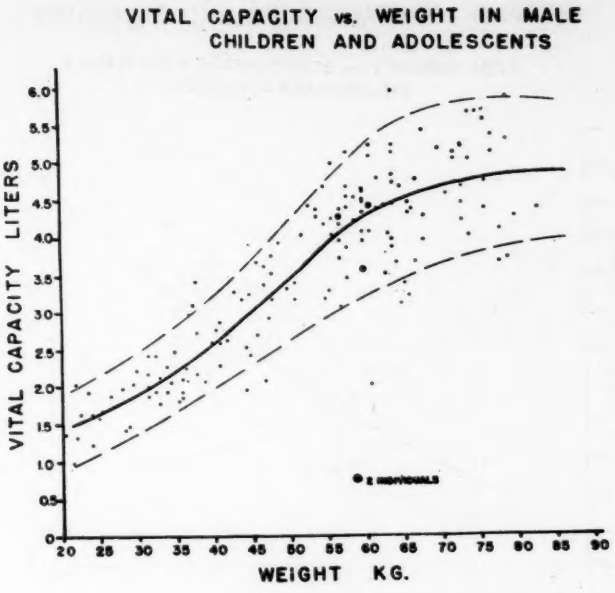

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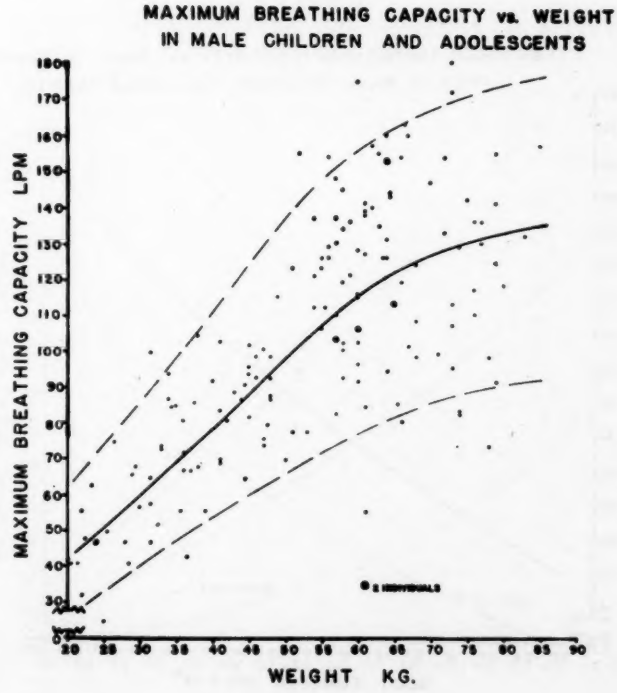

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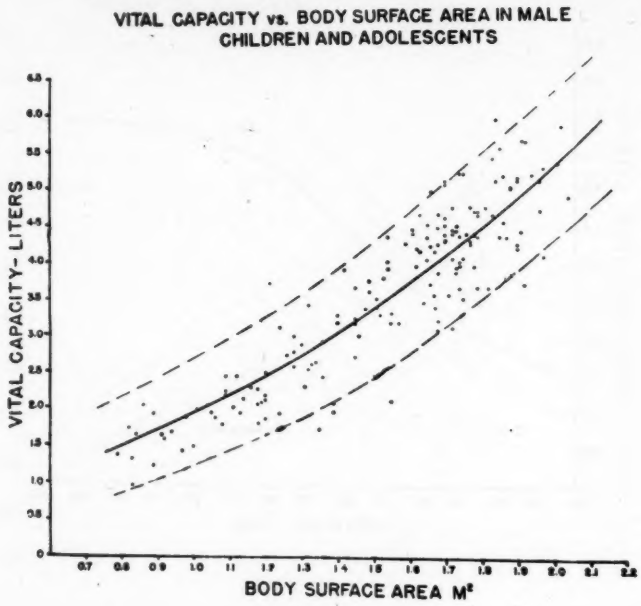

CHART 5

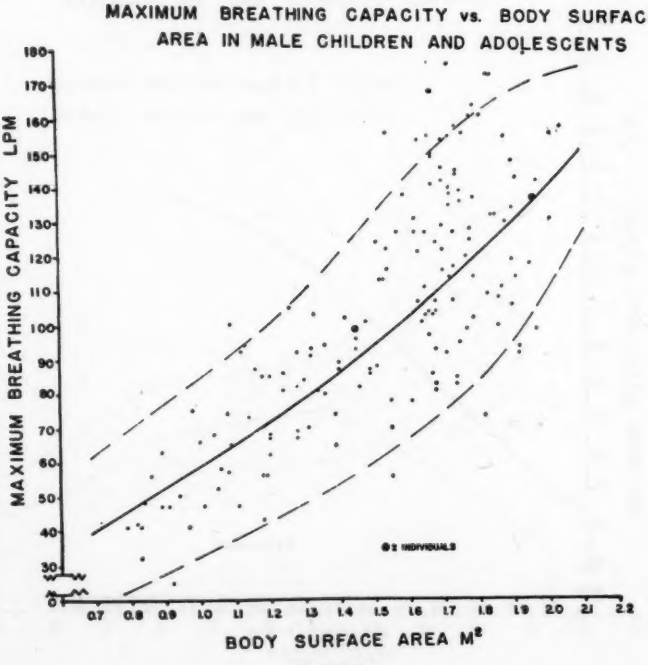
MAXIMUM BREATHING CAPACITY vs. BODY SURFACE AREA IN MALE CHILDREN AND ADOLESCENTS
MAXIMUM BREATHING CAPACITY LPM
BODY SURFACE AREA M²

CHART 6

VITAL CAPACITY vs. HEIGHT IN MALE CHILDREN AND ADOLESCENTS

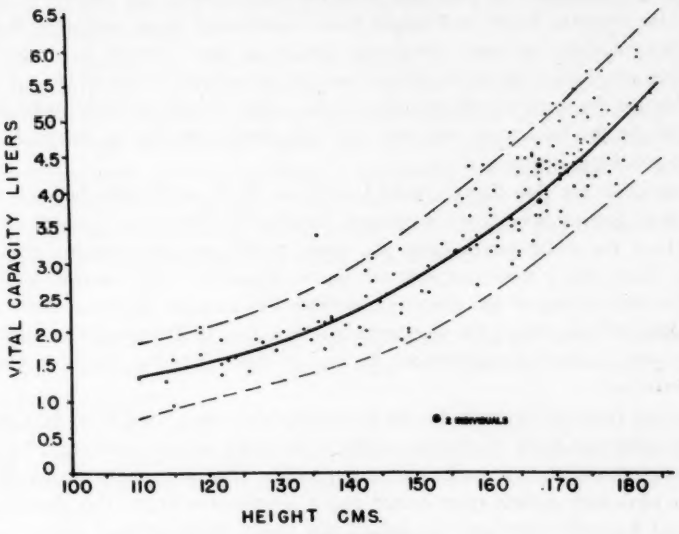

CHART 7

MAXIMUM BREATHING CAPACITY vs. HEIGHT IN MALE CHILDREN AND ADOLESCENTS

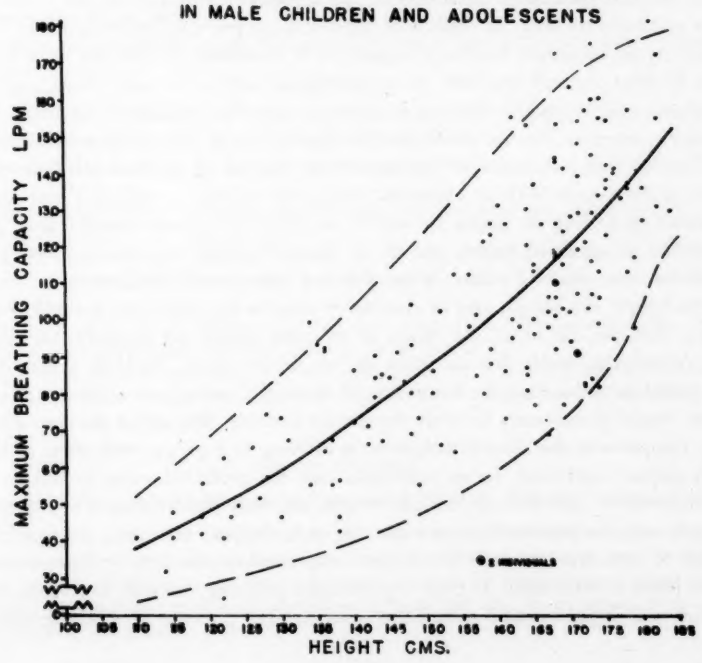

CHART 8

ments it is reasonable to expect that such a change would be present, since the height and weight of an individual are associated with the vital capacity and maximum breathing capacity; the observed height and weight bear a relationship to age similar to that of the vital capacity and the maximum breathing capacity so such a change is not seen when these values are plotted against height and weight. In addition, it should be kept in mind that at this age the spirit of competition and the desire to excel are high: motivation and the will to do the hard work required affect the results obtained in determinations of voluntary breathing capacity.

Another cause for this change could have been due to differences between the two schools. Both groups came from comparable populations. There was a slight overlap in ages between the older group from the lower school and the younger group from Andover. There was a more complete overlap in regard to height, weight, and surface area. It was the feeling of the observer that there was an equal degree of motivation in both groups. In both groups the measurements were done in groups of 3 to 4 persons so that there was a sense of competition. Because of these facts the change in slope is a valid observation.

Wilson and Edwards'[1] formula for the vital capacity in boys (1.902 L. $\times$ M^2) shows no significant difference from the present results in the body surface area range, 0.7 to 1.49 M^2. Beyond 1.50 M^2 their formula gives lower values. This point approximates the range where the adolescent growth spurt occurs, and it is natural to expect this disparity, since Wilson and Edwards[1] calculated the volume per square meter of body surface area and took the mean of their whole age group (6 to 16 years) to obtain a normal value.

Recent observations by Whitfield et al.[6] have shown that the prediction of the vital capacity and the pulmonary subdivisions has a higher coefficient of correlation when multiple attributes are used. To lend more stability to the predicted value of an individual's vital capacity or maximum breathing capacity, it is recommended that the value be based on each of four physical attributes. In an individual with a "normal" shape, any one of the attributes will be equally effective in predicting the vital capacity or maximum breathing capacity; however, the use of the four attributes even in this situation will lend more stability to the final evaluation of the individual. The use of the four attributes is most essential in the person with an abnormal shape, for example, a tall, thin individual. In this instance according to height he would be expected to have measurements greater perhaps than his observed values, and on the basis of weight his predicted values might be lower than the observed values. If the observed value should lie between the predicted values for height and weight and be reasonably close to the values for age and body surface area, then the use of all the values as an index would not penalize this tall, thin person. Admittedly, under this condition the use of the age or the body surface area as indices would be better than the use of height or weight, and a certain amount of clinical judgment would be necessary to select the correct attribute. The use of the four attributes helps to complement the clinical judgment in arriving at a proper evaluation of the abnormally-shaped individual. In an individual case the predicted value should be based upon the predicted value for age, height, weight, and body surface area. It is important to obtain not only the predicted mean value for each attribute but also a range of values which can be considered normal. This range is expressed in the charts by the two standard deviation limits of variability. If there is pulmonary pathology present, low values will be found and will imply lowered pulmonary function. The presence of values greater than

the mean plus two standard deviations has no clinical significance. In individuals having a value below the two standard deviation range there is only one chance in 20 that the value can be considered normal.

In Example 1 (table 10), a patient not in this series, the values are within the expected range for each attribute; whereas in Example 2, another patient not in this series but known to have definite pulmonary pathology, the observed maximum breathing capacity is consistently lower than the predicted values, and in three instances it is outside the two standard deviation limits. There is, therefore, a probability that it is abnormal. The vital capacity is also lower than the predicted values, but it does fall within the expected limits for each attribute and is therefore probably within normal limits. This illustrates in part the greater sensitivity of the maximum breathing capacity test.

Summary

Expected mean values and a range of normal values (plus or minus two standard deviations) are presented for the vital capacity and the maximum breathing capacity of male children and adolescents.

It is recommended that calculations of the above values be based upon four attributes (age, height, weight, and body surface area) rather than upon a prediction deriving from a single attribute (especially in the individual who does not have a standard height and weight for his age).

Acknowledgment

The authors express their indebtedness to Dr. John A. V. Davies and Mrs. C. E. Allen for their courtesy in allowing determinations to be made on students at the Rivers Country Day School in Brookline, Mass.

Appreciation is also due Dr. Jane Worcester for her advice in the statistical evaluation.

References

1. Wilson, M. G., and Edwards, D. J., Vital capacity of lungs and its relation to exercise tolerance in children with heart disease, Am. J. Dis. Child. **22**:443, 1921.
2. Emerson, P. W., and Green, H., Vital capacity of lungs of children, Am. J. Dis. Child. **22**:202, 1921.
3. Robinson, S., Experimental studies of physical fitness in relation to age, Arbeitsphysiol. **10**:18, 1938.
4. Baldwin, E. Def., Cournand, A., and Richards, D. W., Jr., Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects, Medicine **27**:243, 1948.
5. Gray, J. S., Barnum, D. R., Matheson, H. W., and Spies, S. N., Ventilatory function tests. I. Voluntary ventilation capacity, J. Clin. Investigation **29**:677, 1950.
6. Whitfield, A. C. W., Waterhouse, J. A. H., and Arnott, W. M., Total lung volume and its subdivisions: Study in physiologic norms. III. Correlation with other anthropometric data, Brit. J. Soc. Med. **4**:113, 1950.

Spanish Abstract

Capacidad Respiratoria Maxima y Capacidad Vital de Niños y Adolescentes

Los intentos para estudiar el funcionamiento pulmonar de los niños y adolescentes con secuelas poliomielíticas, ha hecho aparente la necesidad de contar con estudios adecuados sobre la capacidad respiratoria máxima verificados en individuos normales. Tratando de obtener estos datos se investigó en 2 escuelas, la capacidad respiratoria máxima y la capacidad vital en un grupo de 161 niños entre 5 y 18 años de edad, sanos y activos.

Los autores presentan cuadros en los que seanotan los valores promedio y las variaciones normalmente encontradas para la capacidad respiratoria máxima y para la capacidad vital.

Ante un caso particular los valores predecibles deben ser calculados teniendo en cuenta la edad, altura, peso y superficie corporal. Es importante no considerar únicamente los valores promedio que corresponden a cada uno de èstos datos, sino también el márgen con que normalmente pueden oscilar. Si existe algún proceso patológico pulmonar, se encontraran cifras menores que implicarán una disminución de la función pulmonar. La presencia de cifras mayores que el promedio o aún mayores que el promedio mas dos derivaciones standard, no tiene significación práctica clínica. Por lo tanto únicamente pueden considerarse, como separándose en forma importante de lo normal, aquellas cifras que se encuentren por abajo del límite inferior de la desviación standard.

Si el individuo es de tamaño promedio, o si no lo es, pero está proporcionado en cuanto a altura y peso, los valores predecibles de acuerdo con cada una de las cuatro características del sujeto que interesan (edad, peso, estatura y superficie corporal) darán resultados similares. Por otra parte, si un individuo es alto y delgado, o bajo y grueso, el cotejo de los resultados obtenidos, con el de los valores teóricos, será mas acertado si se toman en cuenta todas y cada una de las normales en relación con las características mencionadas.

55 Shattuck Street

ADRENOCORTICAL TUMOR ARISING IN THE LIVER OF A THREE YEAR OLD BOY WITH SIGNS OF VIRILISM AND CUSHING'S SYNDROME

Report of a Case with Cure After Partial Resection of the Right Lobe of the Liver

By LAWSON WILKINS, M.D., AND MARK M. RAVITCH, M.D.
Baltimore

THE following case is reported because the occurrence of a virilizing adrenocortical tumor arising within the liver is of importance from the surgical and embryologic standpoint. The authors know of no similar case.

L. T. W. was a boy of 2 yr., 9 mo., when first seen at the Harriet Lane Home. He had been healthy except for atypical pneumonia at the age of 10 mo. and a few sore throats. His growth and development had been entirely normal until 3 mo. before admission. At that time a little hair appeared over the pubis and grew gradually. A week prior to admission, the family physician, Dr. Albert W. Kitts of Salisbury, Md., noted that the penis was larger than normal and in the right upper quadrant of the abdomen a large area of calcification was seen in the roentgenogram.

The boy's height was 90 cm. which was 4.5 cm. less than the average for his age. The weight of 13.6 kg. was normal for his height. He was well nourished and appeared healthy (Fig. 1A). The muscular development was better than average. There was no excess subcutaneous fat and his face was not round or moonlike. Although his color was good, it was not plethoric. No acne and no striae were present. RGs showed an epiphysial development which was normal for his age.

The scrotum was slightly large for his age and showed an adolescent type of wrinkling. Both testes were in the scrotum and were of normal size for his age, measuring 2.1 x 1.1 cm. The penis was definitely enlarged, measuring 8 x 1.5 cm. There was a little fine dark hair over the pubis, 1 cm. in length, but it was not coarse or curly. A prostatic ridge was felt on rectal examination.

The patient's tonsils were enlarged and chronically infected. The lungs and heart were not abnormal. The blood pressure was 80/40 mm.Hg. The liver edge was easily felt 2 or 3 cm. below the left costal margin and extended at this level across the midline. It was smooth and of normal consistency. The spleen and kidneys were not felt.

RGs of the abdomen (Fig. 2) revealed in the right upper quadrant a rounded, mottled calcified mass approximately 6.5 cm. in diameter. The medial border was quite sharp but the lateral margin was poorly defined. In a lateral view of the abdomen the mass was seen to be anterior to the bodies of the 10th, 11th and 12th thoracic vertebrae. Intravenous pyelograms showed a little downward displacement of the right kidney, but the calyces, pelves and ureters of both kidneys appeared normal. Films of the long bones, skull and lungs showed no abnormalities.

The output of urinary 17-ketosteroids* was 11.2 and 9.8 mg./24 hr. on 2 occasions, of which 5.3% was the digitonin-precipitable fraction. The neutral reducing lipids† were 0.19 mg./day. Blood counts and urine examinations were normal. An intradermal test with 0.1 mg. tuberculin was negative. The

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* Ketosteroid excretion was measured by colorimetric estimation with dinitrobenzene in alkaline alcoholic solution.[1]

† The neutral reducing lipids (or "11-oxysteroids") were measured by the phosphomolybdic acid color reaction[2] performed on extracts obtained by chloroform extraction and subjected to benzene-water partition[3] but not Girard's separation.

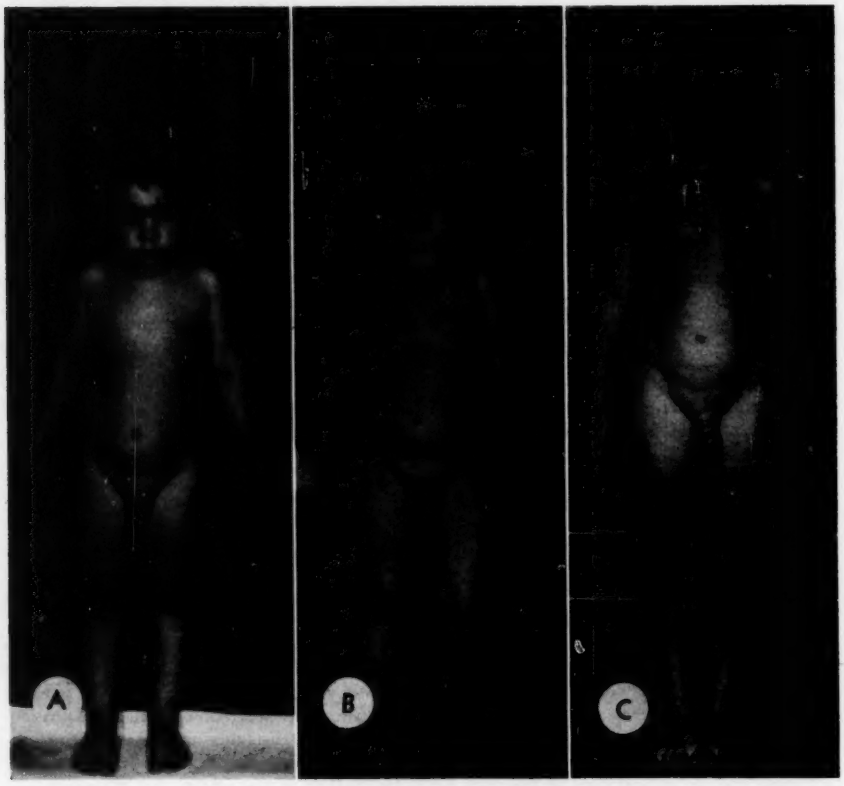

FIG. 1

A	B	C
Age 2¾ yr.	Age 3¾ yr.	Age 4¾ yr.
17 KS. 10 mg./d	immediately after operation	17 KS. 0.8 mg./d

A. One year before removal of tumor. Growth of pubic hair and enlargement of penis had been noted 3 mo. previously. Calcification of tumor shown in Fig. 2.

B. Shortly after removal of right lobe of liver containing adrenocortical tumor. Note that patient has not grown rapidly and that face has become rounder.

C. 11 mo. after operation. Patient has resumed normal growth. Pubic hair has disappeared. 17 KS normal. Patient still well 1 yr. after this.

values of serum NPN, sugar, cholesterol, Ca, P, alkaline phosphatase, total protein, Na, Cl and CO_2 were normal. An oral glucose tolerance test using glucose 1.75 gm./kg. body weight showed elevation of blood sugar to 176 mg./100 cc. at the end of 3 hr. The prothrombin clotting time was 20 sec., which was 65% of normal.

The authors' impression was that the boy had the adrenogenital syndrome and that the area of calcification noted was probably in a tumor of the right adrenal gland responsible for the syndrome.

Operation was performed by Dr. W. W. Scott who has supplied the following description: "The abdomen was opened through a long upper abdominal incision which began above the left crest of the ilium and curved upward to within 4 cm. of the xyphoid. The right adrenal region was explored first and no adrenal gland could be found. Imbedded in the liver was a tumor mass fully 8 cm. in its largest diameter. It did not appear to the operator to be encapsulated and no line of

cleavage was found. A biopsy was taken through what seemed to be the margin of the tumor, but the sections subsequently showed only normal liver tissue. Most of those present at the operation believed that the mass was an adrenocortical tumor which had invaded the liver and was probably malignant. Since it would have been impossible to remove it without resecting the right lobe of the liver, the incision was closed." The postoperative course was uneventful and the patient was discharged 9 days after operation. The parents were told that the outlook appeared hopeless.

During the next 11 mo. the boy remained in excellent health. He was active and vigorous and had a good appetite. His growth did not seem excessive and the mother did not note much change in his sexual development. On examination the blood pressure varied from 80/68 to 138/110 mm.Hg. At that time the output of 17-ketosteroids was 9.1 mg./day. He was admitted to the hospital

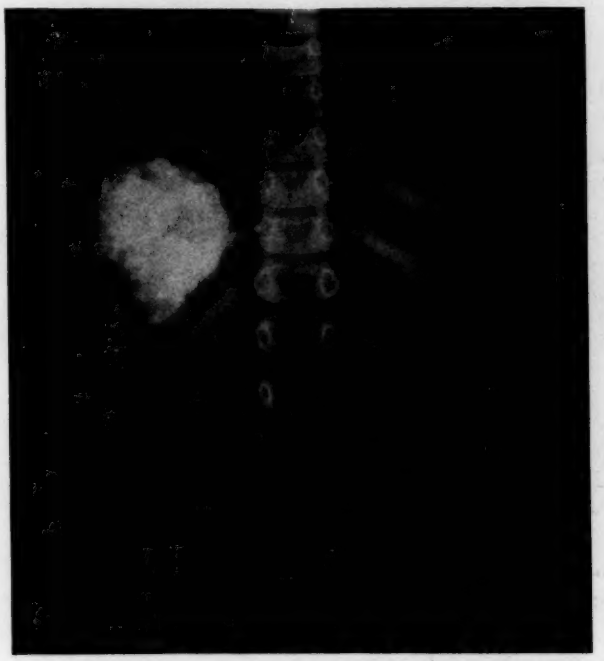

FIG. 2. RG of abdomen showing large calcified mass in position of right lobe of liver.

for re-evaluation of his case at the age of 3 yr., 10 mo. His height was 95.5 cm. which was 6.5 cm. less than the average for his age. The growth of 5.5 cm. during the past year was somewhat less than normal for a boy of his age. The epiphysial development had not advanced abnormally, the average for various centers of ossification being about that of 4 yr. The boy's weight had increased 3.6 kg. and was 2.7 kg. above the average for his height. His appearance had changed (Fig. 1B). His face had become a little fuller and rounder and was quite florid, so that it resembled somewhat the facies of Cushing's syndrome. There were no striae. There was a little acne on his chin. Blood pressure was 108/72 mm.Hg. Pubic hair had grown to 3 to 4 cm. in length and had become coarser and more abundant. There was no apparent change in the penis, scrotum and testes. The output of urinary 17-ketosteroids was 15.8 mg./day, neutral reducing lipids 0.40 mg./day. The condition of the abdomen had not changed. The size of the liver had not increased. No masses were felt. RGs showed that the calcified mass had not changed in size or shape but the calcification seemed more dense and confluent. Films of the long bones, skull, ribs and chest showed no evidence of metastases.

The finding that growth and osseous development were not progressing abnormally rapidly and

that the patient was becoming gradually obese with a more round florid face, suggested that the hormonal manifestations now were more of the type found in Cushing's syndrome than of those occurring in the adrenogenital syndrome. Since the tumor apparently had not grown or metastasized, it was considered that it might be relatively benign and that its removal with resection of a portion of the liver should be attempted.

The second operation was performed 22 days after admission by Drs. Mark M. Ravitch and W. W. Scott. The old transverse incision was re-opened for its full length and extended out into the right flank. There was an enormous stony hard mass occupying most of the right lobe of the liver and extending up from the region of the right kidney to the dome of the diaphragm. One could freely pass one's hand behind the liver at the same time passing it completely behind the tumor so that it

FIG. 3. Right lobe of liver together with tumor entirely buried within it. Note heavy silk which was used for 2 rows of mattress sutures between which liver was divided.

seemed that the tumor was entirely within the substance of the liver. It appeared that it would not be possible to dissect out the tumor but that the right lobe of the liver would have to be taken with it. In order to provide more exposure, 4 costal cartilages were removed on the right so that the retractor would be pulling against nothing more rigid than the musculature of the abdominal wall and the diaphragm. This gave wide exposure of the right lobe of the liver which could be brought well down into the wound. The medial border of the tumor, while fairly close to the region of the porta hepatis, certainly did not involve the porta and it seemed possible to place a line of sutures medial to the tumor without compromising the circulation of the liver. The gallbladder was freed from the liver and left attached only to the cystic duct and cystic artery. With a large surgeon's needle heavy silk mattress sutures were placed through and through the liver in pairs from front to back and the liver was gradually cut through between pairs of such sutures going through the full thickness of the right lobe of the liver fairly close to the midline. The great thickness of the liver in this portion offered some difficulty in the placement of the sutures but this was surmounted without the occurrence of severe blood loss at any time. When the liver was entirely cut through it was found that there was absolutely no connection between the tumor and the vena cava and that the only connection left to the right lobe of the liver and the tumor mass was a little scar tissue connecting it to the renal capsule in the region of the upper pole. This seemed obviously to be the residuum of the previous operation. This scar was cut through with a knife. No tumor was recog-

nized and no bleeding occurred. There was certainly no question at the time of this operation but that the tumor derived its entire blood supply from the liver and was entirely within the hepatic substance. The left kidney felt normal and the left adrenal was palpable but the operation was not prolonged for an actual exposure of the left adrenal. A large sheet of gel foam was plastered down on the extensive raw surface of the liver and a Penrose drain was placed up into the subphrenic space. The child's condition remained good throughout the 2½ hr. procedure during which he received 1500 cc. blood.

The appearance of the tumor is shown in figures 3 and 4. It measured 5 x 5.5 x 6 cm. and occupied most of the right lobe of the liver. It was surrounded by a thick well defined capsule which seemed intact. The tumor was completely imbedded in liver tissue except for a small area on the

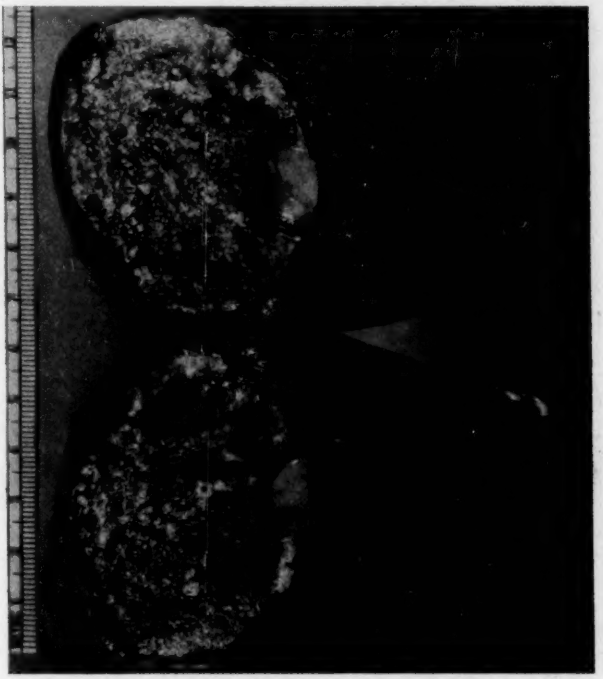

FIG. 4. Specimen bisected sagittally showing tumor completely surrounded by liver. Photomicrograph in Fig. 5 is section taken through most superficial portion of tumor.

posterior surface where it appeared to be covered only by capsule. Even here microscopic examination showed what appeared to be compressed liver cells and bile ducts overlying the capsule (see Figs. 4 and 5). No arteries or veins were found entering the tumor from outside of the liver. On cut section the tumor was of yellowish color and was gritty due to calcium depositions in necrotic tissue. Dr. Stanton Eversole of the Department of Pathology has furnished the following description of the microscopic appearance: "The tumor is composed of cells varying greatly in size and shape. The cytoplasm is finely granular and stains eosinophilic with varying intensity (Figure 6). There is little or no lipoid in them. The nuclei vary greatly in their structure and staining. Many vacuolated nuclei are present. In numerous areas of necrosis calcium deposits are noted. The cells grow in solid masses for the most part, but in places large cells lie in a loose stroma. The surrounding liver tissue is separated by a fibrous capsule and the former has undergone varying degrees of pressure atrophy (Figures 5 and 7)."

Postoperative course: Preparatory to operation the patient was given lipoadrenal extract and testosterone propionate by intramuscular injection. During the operation he received intravenously 1500

FIG. 5. Low power view (x80) of point at which tumor is closest to surface of liver, showing thin but continuous band of liver tissue superficial to dense fibrous capsule which surrounds tumor. There is some fibrin on surface of liver.

cc. citrated blood and glucose and salt containing aqueous adrenal extract. Following operation intravenous drip of glucose and salt was continued. He remained in good condition during and after operation until 8 or 9 hr. later when the pulse became rapid and the blood pressure fell. By the following morning his pulse could not be felt and the heart sounds could scarcely be heard. The serum Na was 132 mEq./l. and the K 3.8 mEq./l. It was felt that his condition was one of surgical shock caused by inadequate replacement of the fluids lost at operation and particularly the subsequent loss from the huge parenchymal and parietal wound surfaces. He was placed in an oxygen tent, digitalized with cedilanid and given 250 cc. plasma rapidly. This was followed by another 250 cc. plasma and 250 cc. whole blood. His condition improved but during the day the right chest filled with bloody fluid. Thoracentesis of 370 cc. gave considerable relief. The serum sodium was 138 and the potassium 4.2 mEq./l. Thoracentesis was repeated on the second postoperative day and he was given another 225 cc. plasma. He drained a moderate amount of serous fluid from the abdominal wound but little or no bile. During this time he was treated with penicillin and streptomycin and received aqueous adrenal extract, lipoadrenal and testosterone propionate. The hormonal therapy was probably excessive as on the third postoperative day the serum potassium had fallen to 2.7 mEq./l. and the CO_2 was 37.6 mEq./l. The serum Na was 134 mEq./l. and the Cl 86 mEq./l. No edema was apparent. He was given 54 mEq. potassium chloride by mouth and he was fed orange juice. After the fourth day there was gradual improvement in his general condition. However, his temperature varied between 40 and 41°C. for 17 days and fell gradually to normal by the 27th day. Thrombophlebitis and cellulitis at the "cut down" site were partly responsible for the fever. The abdominal wound healed

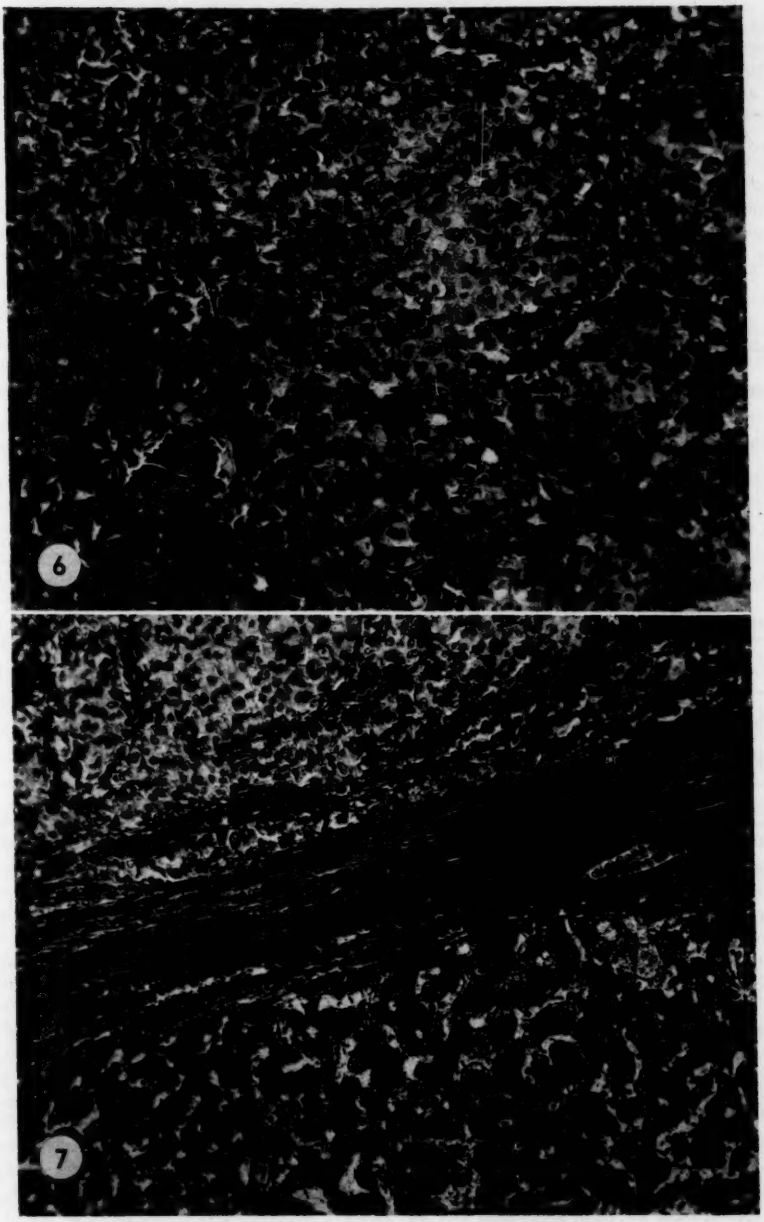

FIG. 6. Adrenal tumor within liver (x150). Tumor is composed of large clear cells with some tendency toward arrangement in strands or fasciculi separated by fibrous septa. Note area of calcification in lower left.

FIG. 7. (x150) Tumor (above) is separated from liver (below) by dense fibrous capsule.

per primam and several attempts at aspirating any subphrenic collection of fluid were fruitless. Adrenal hormones and testosterone were discontinued on the 13th postoperative day. Following operation the output of urinary 17-ketosteroids fell to approximately 0.5 mg./day. After discontinuance of the hormonal therapy his chubby, plethoric appearance disappeared and he was discharged from the hospital.

After his return home, the patient's appetite became poor. At times he complained of abdominal pain. The parents coaxed and forced him to eat and he occasionally vomited. Twenty-one days after discharge, he began to have a fever which reached as high as 39°C. The appetite became worse. From time to time there was a slight skin rash. On readmission to the hospital 6 days later, his appearance had changed greatly. His weight had dropped from 17.3 to 15.6 kg. His face was slender and pale. Pubic hair, which had been shaved, had regrown. The 17-ketosteroid excretion was 0.4

TABLE 1

Date	12-27-49	1-4-50	1-12	1-19	1-27	3-14	4-24	6-19
Cephalin flocculation	3 plus	3 plus	3 plus	3 plus	3 plus	0	0	0
Thymol turbidity (units)	22	27	16	19.5	14.3	2.8	3.4	2.3
Bilirubin—total (mg./100 cc.)	1.5	8.8	3.0	3.0	1.0	0.8	0.8	0.8
Direct (mg./100 cc.)	1.1	6.0	0.8	0.8	0.8			
Alk. phosphatase (B.U.)	29.8	27	16	12.8	16	12.6	14.8	16.6
Total Protein (gm./100 cc.)	6.6	5.9	7.4	7.6				6.7
Albumin	3.3	3.3	4.4	4.4				4.6
Globulin	3.3	2.6	3.0	3.2				2.1
Sed. Rate (corrected mm./hr.)	18	34			34		16	10
17 Ketosteroids (mg./day)	0.4		0.7			0.9	1.3	0.8

mg./day. The liver had become larger, the edge extending 4 cm. below the xyphoid and to the left. It felt firm but was smooth and no nodules were felt. No jaundice was apparent although on one occasion the bilirubin of the serum was reported as 8.8 mg.%. He continued to have irregular temperature fluctuations between 36 and 38°C. (rectal). The blood counts were within normal limits. The sedimentation rate was increased. The concentration of serum NPN, Na, K, Cl, CO_2, Ca and P were normal. Studies related to liver function revealed impairment. These are shown in table 1. An acute illness manifested by evidence of hepatic damage appeared to have supervened. It seemed improbable that the liver damage was the result of metastases or invasion of the adrenal tumor because the ketosteroid excretion remained constantly low. The possibility that his illness was due to extensive degeneration or necrosis resulting from operative interference with the circulation of the liver was considered and dismissed as unlikely in view of the known regenerative power of the liver. The fact that the patient had received large amounts of plasma and whole blood and that the onset of symptoms occurred within the appropriate period suggested that the patient had serum hepatitis, and this was borne out by his future course. Treatment was directed toward maintaining satisfactory nutrition. During the early part of the hospital stay the patient's appetite was poor and he vomited if coaxed or forced. The appetite improved and his diet was increased gradually and supplemented with vitamins. The course of the hepatitis was relatively benign and at no time was jaundice obvious. He was allowed to return home after 6½ wk. and 1½ mo. later was permitted to be out of bed. His cephalin flocculation dropped from 3+ to 0, thymol turbidity from 22 to 2.8 units, bilirubin from 8.8 to 0.8 mg./100 cc. and alkaline phosphatase from 29.8 to 12.6. Improvement continued. Three months later, a tonsillectomy was performed. Since then his health has been excellent.

Following operation the pubic hair which had been shaven had grown again, reaching a length of

1 to 1.5 cm. and 1½ mo. after discharge it was clipped off. One and a half months later, about 20 to 30 short dark hairs 0.5 cm. in length were present. Two months later, there was only a little fine, blond fuzz and this has not increased since. The penis became somewhat smaller and remained constantly flaccid, whereas before operation erections occurred frequently. The 17-ketosteroid excretion had remained at levels between 0.5 and 0.8 mg./day. His appearance 7 mo. after discharge is shown in Fig. 1C. His growth has continued within normal limits. When he was 5 yr., 10 mo. of age, his height was 119.5 cm. which is the average for a boy of 7 yr. The bone age was 6 yr. There were no evidences of metastases in the bones or lungs. The 17-ketosteroids were 1.6 mg./day. He had lost entirely his virile, thick-set florid appearance and looked like a slender normal boy of his own age.

Discussion

The occurrence of an adrenocortical tumor within the liver is most unusual and of interest from the embryologic standpoint. The right adrenal gland was absent, and the tumor in the right lobe of the liver did not have circulation through an adrenal artery or vein nor any vascular attachments to the vena cava or renal vessels or renal parenchyma, but was nourished through the hepatic circulation. These findings indicate that the neoplasm arose from aberrant adrenal cells within the liver tissue and did not develop in an adrenal gland and then invade the liver. The authors found it difficult to understand how adrenal cells could be misplaced in the liver, since this organ develops from an outbudding of the gut whereas the adrenal develops in the adrenogenital ridge posterior to the coelom. However, embryologists have pointed out that in the early embryo the gut is suspended in the coelom by the mesogastrium, a fold of the coelomic lining. The foot of the mesogastrium lies along the adrenogenital ridge. At this early embryonic stage cells from the adrenogenital ridge could migrate along the mesogastrium toward the gut and be included in the developing anlage of the liver.

Rare as such an instance may be, the possibility of the occurrence of a hormone-secreting adrenocortical tumor in the liver presents one more argument in favor of the transperitoneal approach in exploratory operations for such tumors. If renal displacement, calcification, laminographic shadows or pyelographic studies do not localize the tumor, a transverse transperitoneal incision offers the best opportunity for exploration of the possible locations of such a tumor. At the same time the actual resection is better done through such an incision than through any other save the more extensive thoraco-abdominal approach. One of the authors (M.M.R.) elects to resect appropriate costal cartilages to give pliability to the upper wound edge and provide maximal exposure.

Summary

A case is reported of a boy of 3 years, 9 months, who presented the features of the adrenogenital syndrome. RGs showed a large calcified mass in the right upper quadrant of the abdomen. This proved to be a virilizing adrenocortical tumor, buried in the right lobe of the liver and receiving its circulation throughout the liver. Resection of four costal cartilages gave direct access to the liver through a transverse abdominal incision without the necessity for division of the diaphragm and permitted successful removal of the tumor and most of the right lobe of the liver. The tumor had no attachments to the right kidney or vena cava. There was no adrenal tissue in the usual location on the right. The child is well and developing normally two years after operation.

Acknowledgments

The authors wish to thank Drs. Robert Klein and Roger A. Lewis and the members of the resident staff of the Harriet Lane Home for the careful attention given this patient.

REFERENCES

1. Callow, N. H., Callow, R. K., and Emmens, C. W., Colorimetric determination of substances containing grouping—CH_2CO—in urine extracts as indication of androgen content, Biochem. J. **32**:1312, 1938.
2. Heard, R. D. H., and Sobel, H., Colorimetric method for estimation of reducing steroids, J. Biol. Chem. **165**:687, 1946.
3. Talbot, N. B., Saltzman, A. H., Wixom, R. L., and Wolfe, J. K., Colorimetric assay of urinary corticosteroid-like substances, J. Biol. Chem. **160**:535, 1945.

SPANISH ABSTRACT

Tumor Adrenocortical de Punto de Partida Hepático en Un Niño de 3 Años y 9 Meses de Edad

Presentación de un caso con curación después de la resección parcial del lóbulo derecho del hígado

Loos autores creen que es importante el siguiente caso porque un tumor adrenocortical virilizante, de punto de partida hepático, es de interés tanto desde el punto de vista quirúrgico como del embriológico. No tienen conocimiento de algún otro caso similar.

Examinando por primera vez en octubre de 1948 a los 2 años 9 meses de edad, se proporcionaron como datos importantes los de iniciación del padecimiento 3 meses antes con aparición y crecimiento gradual de pelo púbico, crecimiento peneano y área calcificada apreciable a la radiografía, en el cuadrante superior derecho del abdomen. A la exploración física se encontró pene francamente aumentado de tamaño, pelo de color obscuro sobre pubis y prominencia prostática apreciable al tacto rectal. El borde hepático fué fácilmente palpable 2 a 3 cms. por abajo del borde costal. La placa lateral de abdomen reveló una sombra moteada calcificada, situada por delante de la décima, undécima y duodécima vertebras torácicas. La eliminación urinaria de 17 ketoesteroides fué de 11.2 y 9.8 mlgs por 24 horas. La impresión fue la de que el niño tenía un síndrome adrenogenital y que el área de calcificación correspondía probablemente a un tumor de la suprarrenal.

Se realizó una intervención quirúrgica en noviembre de 1948 encontrándose que nó se podía localizar a la suprarrenal derecha y que en el hígado mismo había una tumoración como de 8 cms. en su diámetro mayor, que no parecía estar encapsulado y de la cual se tomó una biopsia que subsecuentemente solo mostró tejido hepático normal. La opinión que prevaleció fué de que se trataba de un tumor adrenocortical, probablemente maligno, que había invadido el hígado, por lo que se cerró la incisión y se dió de alta al enfermo en noviembre de 1948 haciendo saber a los familiares el pobre pronóstico del padecimiento.

En los siguientes 11 meses el niño permaneció en excelente estado de salud y sin cambios acentuados en su desarrollo sexual. En febrero de 1949 la excreción de 17 ketoesteroides fué de 9.1 mlgs. diarios y la presión arterial varió entre 80/68 y 138/110 mm. de mercurio. Fué admitido en octubre de 1949 a los 3 años 10 meses de edad con el objeto de re-evaluar su caso. Se encontró que tenía facies redonda y florida semejante a la encontrada en el síndrome de Cushing. Había discreto acné en el mentón. Ni el tamaño del hígado ni la sombra calcificada habían variado, como tampoco lo había hecho el tamaño del pene, escroto o testículos. No se evidenciaron metástasis. Los 17 ketoesteroides en la orina fueron 15.8 mlgs. por día. Las manifestaciones hormonales encontradas estaban de acuerdo más bien con un síndrome de Cushing que con el síndrome adrenogenital, considerándose que podía intentarse la eliminación de la tumoración resecando una porción del hígado.

En la segunda intervención se encontró una tumoración de consistencia petrea que ocupaba la mayoría del lóbulo derecho del hígado y se extendía desde la región del riñón derecho hasta la cúpula diafragmática, estando totalmente incluída dentro de la substancia hepática. La resección de 4 cartílagos costales dió una mayor facilidad de acceso sin necesidad de dividir el diafragma y permitió la eliminación del tumor, previa resección de la mayoría del lóbulo derecho del hígado. El estudio microscópico reveló células de diversos tamaños y formas, con citoplasma finamente granular que aceptaban la coloración eosinofílica con diversa intensidad. Contenía muy poca o ninguna substancia lipoide. El núcleo varió grandemente en su estructura y en tinción, existiendo

muchos de ellos con vacuolas. En numerosas áreas de necrosis habia depósitos de calcio. Las células formaban agrupamientos compactos, solo en algunos sitios habia algunas células grandes poco adheridas al estroma. El tejido hepático estaba separado del tumor por una cápsula fibrosa.

El choque quirúrgico post-operatorio requirió tienda de oxígeno, digitalización y transfusiones de plasma y sangre. Se necesitaron 2 paracentesis de hemitórax derecho para haberse llenado este de un líquido sanguinolento. Fué tratado además con penicilina y estreptomicina y recibió extracto acuoso suprarrenal, lipoadrenal y testoesterona. La temperatura se abatió hasta el veintisieteavo día. En diciembre de 1949 fué readmitido al Hospital ya que su estado general había empeorado, suponiéndose que el enfermo tuvo una hepatitis por suero homólogo, a pesar de que la ictericia nunca fué un dato prominente. Mejoró bajo tratamiento dirigido fundamentalmente hacia el mantenimiento de un estado nutricional satisfactorio y continuó posteriormente y hasta la fecha, en excelentes condiciones. Para junio de 1950 el pelo púbico habia casi desaparecido, el tamaño del pene se había reducido y la excreción de 17-ketoesteroides se encontraba dentro de límites normales. A los 5 años 10 meses de edad, la edad ósea era de 6 años y su aspecto era el normal para un niño de esa edad.

Los autores sugieren que el neoplasma se produjo por células suprarrenales aberrantes.

The Johns Hopkins Hospital

HEREDITARY SEXUAL PRECOCITY

Report of a Family with 27 Affected Members

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PRECOCIOUS somatic and sexual development of the "constitutional" type is not common in males and its familial occurrence is rare, only five instances having been recorded.[1-5] It seems worth while, therefore, to report a family in which 27 individuals are known to be affected by this condition.

Through the cooperation of a member of the family it has been possible to obtain in writing a certain amount of information about each affected individual, and this is summarized below. When data about a patient could be obtained from his physician, a more complete report is included. Brief summaries are given of the previously published case reports of three members of this family. (See chart 1.)

CASES

1. Early sexual and physical development. Mature ht. 160 cm., wt. 70.3 kg. Died at 65 yr.
2. Large physically from 2 to 12 yr. Pubic hair appeared at 3 yr. Mature ht. 160 cm., wt. 70.3 kg. Died at 60 yr.
3. Early sexual and physical development. Pubic hair appeared at 5 yr. Mature ht. 162 cm., wt. 90.7 kg. Died at 61 yr.
4. Early sexual and physical development. Accidental death at 4 yr.
5. Early sexual and physical development. Mature ht. 154 cm., wt. 63.5 kg. Died at 55 yr.
6. Early sexual and physical development. Pubic hair appeared at 4 yr. Mature ht. 160 cm., wt. 72.6 kg. Died at 64 yr.
7. Early sexual and physical development. Pubic hair appeared at 3 to 4 yr. Mature ht. 157 cm., wt. 61.2 kg. Died at 61 yr.
8. Early sexual and physical development. Pubic hair appeared before 7 yr. Mature ht. 167 cm., wt. 77.1 kg.
9. Early sexual and physical development. Pubic hair appeared at 2 yr. Extremely strong in youth; at age of 4 yr., he carried his father who weighed 81.6 kg. (Photograph and article appeared in newspaper.) Died at age of 58 yr.
10. Early sexual and physical development. Did not increase in height after 10 yr. Mature ht. 154 cm., wt. 70.3 kg.
11. (This case was reported by Rush et al.[3]) Examined at age of 33 yr.: ht. 162 cm., wt. 52.1 kg. Sex development said to have been "complete" at age of 5 yr. Sang bass as a lad, but since age of 25 yr. sings tenor. Grew fast but stopped at age of 14 yr. Complete hospital investigation revealed essentially normal individual.
12. Early sexual and physical development.
13. Early sexual development. Pubic hair appeared at 2 yr. Mature ht. 160 cm., wt. 61.2 kg.
14. Early sexual and physical development. Pubic hair appeared between 2 and 3 yr. Mature ht. 152 cm., wt. 61.2 kg.
15. Early sexual and physical development.
16. Early sexual and physical development.

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17. Early sexual and physical development. Pubic hair appeared between 7 and 8 yr. Mature ht. 175 cm., wt. 61.2 kg.

18. Early sexual and physical development. Ran away from home at age of 9 yr., stayed away for 6 mo., and "was nearly married." Mature ht. 165 cm., wt. 63.5 kg.

19. Early sexual and physical development. Pubic hair appeared between 3 and 4 yr. Dr. C. Kelly Canelo of San Jose, Calif., writes as follows:

"This boy came under my care on July 13, 1934. He was brought to my office for medical advice regarding his stature. It seems that they were desirous of his eventually taking up a military career and were quite fearful of the fact that he might not attain sufficient stature.

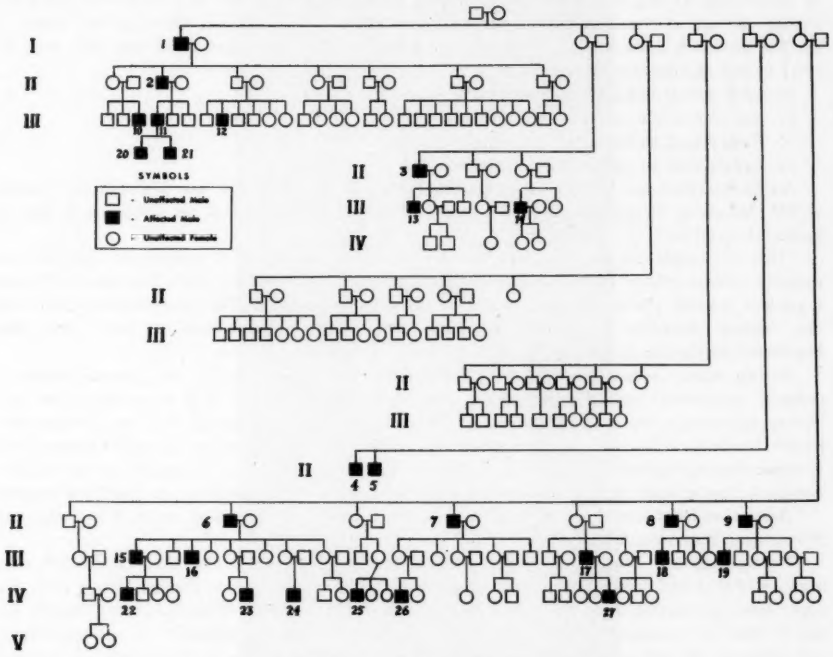

CHART 1. Pedigree. Numbers refer to cases in text.

"At the time I first saw the boy he was under 12 years of age. His height was 166 cm. and he showed rather marked muscular development, definite growth of mustache and beard, some deepening of his voice, some axillary and pubic hair and genitalia that would be normal for an 18 yr. old boy. In addition to the routine laboratory work we had bone-age studies done and they showed all epiphyses closed (elbows, wrists, femur and crest of the ilii). I advised them at that time that further growth was not possible; at least not more than a fraction of an inch at the most. They insisted that we undertake all possible treatment. Accordingly he was treated for the next year with various anterior pituitary preparations. At the end of one year there was no evidence of further growth so I insisted that we abandon treatment.

"It is of interest to note that in November 1937 he was examined for life insurance and at that time his height was 170 cm. with his shoes, so no further growth took place. (This information was obtained from the medical director of the New York Life Insurance Company.)"

20. (This case was reported by Rush et al.[2]) Examined at the age of 8 yr. Ht. 168 cm., wt. 39.9 kg.

At about the age of 18 mo. external genitalia began to develop rapidly and pubic hair began to grow. At 2 yr. of age his general body growth seemed accelerated. At 6 yr. pubic hair was

abundant, axillary hair was present, and the beard began to grow necessitating shaving. He became sex-conscious and emissions occurred.

In the Doernbecker Hospital at the age of 8 yr., he appeared the size of a 16 yr. old boy. The urine was extracted to obtain the prolan content. This was tested on immature female white rats and the result was negative. The urine was also extracted to obtain the male sex hormone; this extract was tested upon the capon for comb growth and the result was positive.

21. (This case was reported by Rush et al.[3]) Examined at the age of 5 yr.; ht. 126 cm., wt. 23.1 kg. Seen first in Doernbecker Hospital at age of 4 yr., when it was noted he was large for his age, had a deep voice and that the external genitalia were markedly developed with a beginning growth of pubic hair. At 4½ yr. mother began shaving his mustache every few days to prevent childhood teasing. At age of 5 yr., penis, scrotum and testes were fully developed. Bone age was about 12 yr. The urine was extracted to obtain male sex hormone; this extract was tested upon the capon for comb growth and the reaction was positive.

22. Early sexual and physical development.

23. Early sexual and physical development.

24. Early sexual and physical development.

25. Early sexual and physical development.

26. Early sexual and physical development. Pubic hair appeared at 8 mo. Through the courtesy of Dr. Morris L. Bridgeman of Portland, Ore., the following record of his admission to Doernbecker Hospital in 1941 was obtained:

"This 17 month old boy was well and normal up to the age of 8 months. At that time the patient's parents noticed that there was a beginning growth of pubic hair. Since that time he has had a gradual sexually precocious development of the external genitalia. The penis, scrotum and testes have become adult-like in size and appearance. Patient has frequent erections which have been manifested for the past month.

"Family history reveals that the mother and father are in good health. One paternal cousin is mentally precocious. Physical examination discloses a well developed, well nourished white boy. General appearance, especially the facies, is of a boy older than the stated age. His voice is somewhat hoarse. He has a full set of deciduous teeth, spaced far apart. The nose has an adult figuration and is larger than the normal nose. There is a moderate growth of pubic hair. The penis is large and circumcised. The testicles are both enlarged, and in the scrotum. The extremities are short and squatty.

"Admission laboratory work revealed normal urine, and a normal blood count. Tuberculin and Wassermann tests were negative.

"Roentgenograms: Skull normal, with no enlargement of the sella. Flat plate of the abdomen, negative. Pelvic and hip bones normal. Upper extremities show no bone changes. Heart is in the upper limits of normal, as to size. Lung fields are clear. Epiphyseal development is in a slightly advanced state in comparison with the child's age of 17 mo. While the epiphyses for the metacarpals and phalanges do not appear normally until 3 yr. of age, most of the child's are already present. In addition the head of the humerus usually shows only one epiphyseal center at this period, while this child has 2 rather well developed centers. Most of the epiphyseal plates for the metatarsals and phalanges of the foot are also present. (These usually do not appear until 3 yr. of age.)

"The hospital course was entirely uneventful until the 5th hospital day when his temperature arose to 40.0° C. Physical examination at that time was negative. Temperature dropped to normal after about 24 hours, and remained flat thereafter.

"The diagnostic possibilities considered included pineal tumor, adrenal tumor, adrenal hyperplasia and familial precocity."

Dr. Bridgeman writes on 10/10/49:

"This boy is now 10 yr. old and whereas he was an extreme problem in the neighborhood around the age of 4 or 5 yr., he has made a fairly good adjustment. He is getting along with his companions very well and was a member of a cub pack, finally becoming den chief.

"I recently studied him in my office at which time x-rays of skull showed no malformation. His bone age was markedly advanced and his stature, whereas advanced for his age, indicates he will be a small adult."

27. (See Fig. 1.) Early sexual and physical development. Summary of admission to Children's Hospital of Buffalo at age of 3 yr. is as follows:

"There is no history of infantile deaths in the family due to sudden collapse or associated with

symptoms of intestinal obstruction, such as may occur in adrenal cortical deficiency. This 2 yr., 11 mo. old white male, born June 29, 1946, is admitted to this hospital for investigation because of enlargement of the penis which has been noted since the age of 1 yr. Patient was normal at birth weighing slightly over 2.7 kg. He had no neonatal distress of any kind—no vomiting, no collapse and no polyuria. Patient appeared normal to parents until 1 yr. of age when penis was noted to

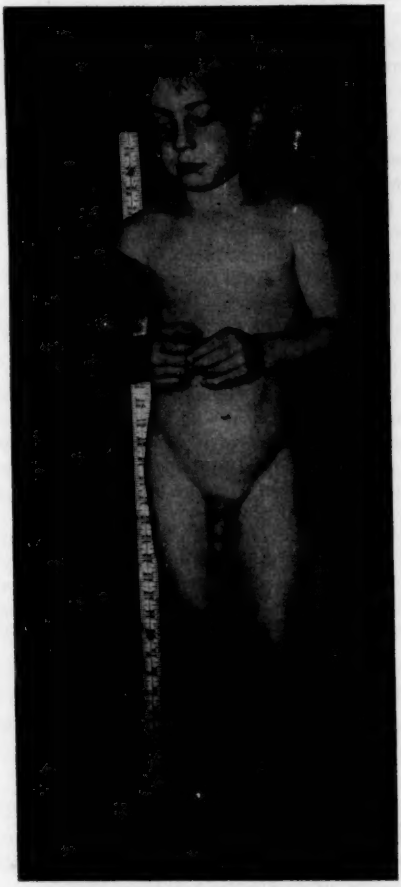

FIG. 1. Case 27 at age of 2 yr., 10 mo.

be large. He weighed 10.4 kg. There was no pubic hair at this time. He continued to do well. One month ago pubic hair appeared.

"Patient has experienced no headache, polyuria or polydipsia. Mother states that he does not object to a large salt content in food and not infrequently licks the salt shaker. He has had no spells of weakness. His mental development seems normal for a 3 yr. old. There are 2 sisters who are normal.

"Physical Examination: Pulse 80/min.; respirations 20/min.; temperature 37.5° C.; blood pressure 95/60 mm.Hg; ht. 104 cm.; wt. 18.6 kg.

"General Appearance: Patient is an overly developed male who has a somewhat dull expression on his face but is cooperative and who has the appearance of a 6 yr. old in size. Musculature is large and powerful.

"The genitalia have the appearance of those of a 14 yr. old. Pubic hair is present. There is a large penis and large testes.

"Laboratory Findings: Urinalysis—negative. Blood examinations: Hgb. 13.6 gm./100 cc.; RBC count 4.3 million/cmm.; WBC 7.5 thousand/cmm.; neutrophils 46%, bands 10%, lymphocytes 40%, eosinophils 1%, monocytes 3%, BUN 14 mg./100 cc.; Serum Cl 97 mEq./l., Ca 8 mg./100 cc., P 6.5 mg./100 cc., phosphatase 7.8 Bodansky units.

"Glucose tolerance test showed a normal curve.

"Roentgenographic examination: Skull appears normal. Abdomen negative. Long bones appear normal. Bone age is approximately 6 yr., 3 mo.

"Urinary 24 hr. 17-ketosteroids—0.

"Impression: Because testes are enlarged to same degree as penis, indicating general anterior pituitary stimulation (rather than atrophic as in primary adrenal cortical stimulation) adrenocortical syndrome is unlikely. Absence of high 17-ketosteroid excretion bears this out.

"Impression: constitutional sexual precocity.

"Laboratory tests (Dr. Fuller Albright):

11/30/50: Test for FSH in urine—Less than 6.5 mouse units/24 hr.

1/27/51: Test for 17-ketosteroids in urine: 0.9 mg./24 hr.

3/12/51: Test for FSH in urine: Less than 13 mouse units/24 hr.

Psychologic examination at 4 yr. of age: C.A. 3 yr., 11 mo.; M.A. 5 yr., 1 mo.; I.Q. 130. (This rank is in the lower range of the Very Superior Group according to the Terman classification of mental ability.)"

A summary of the psychologist's report is as follows:

"Bobby responded in a rather mature fashion while in the office. He was perfectly willing that his parents go downstairs and wait for him while he remained to work with the examiner. He attended well, carried out directions to the letter, and evidenced no hyperactivity common to many children of today. He was relatively free from distraction by extraneous stimuli.

"The teacher of a small country school which he had been attending for several months (having been tutored at home up to this time) said he was reading very well on the first grade level and that his work in numbers was quite satisfactory. He played well with other children.

"He will be promoted to 2nd grade in June. This will mean 2 yr.' acceleration in school.

"As regards maturity, Bobby fluctuates between being a 4 yr. old and a 6 or 7 yr. old child. I was quite impressed by his behavior one evening when I called at the home. He became tired, went quietly upstairs, undressed himself and went to bed, without the directions of either parent. This from a 4 year old!"

In adulthood all these individuals are normal, the only deviation being a tendency to shortness of stature. Of those whose adult height could be ascertained, more than half were 160 cm. in height or less. They were of average longevity.

Heredity

In analyzing the pedigree we start with the following facts:

1. The trait is not lethal, since most of the individuals live to maturity.
2. The marriages between affected males and their wives were not consanguineous (so far as careful inquiry has been able to determine).
3. The trait is rare.
4. It has affected males exclusively in this family.

Bearing this in mind, the pedigree may be analyzed for the simple modes of inheritance. The trait has affected males exclusively in this family. This is not because it is able to affect structures found only in the male; sexual precocity could equally well be manifested in the female, but in this family females remain normal. We must, therefore, look to the modes of inheritance which permit one sex only to be affected in order to explain its sex limitation.

The following must be considered:

A. Sex linkage that is carried on the nonhomologous segments of the sex chromosomes, either as a dominant or a recessive.

1. Carried on the Y chromosome, necessarily as a dominant, it affects only males. It affects all sons of affected fathers, and never appears in the male child related to the family through the female line. Both criteria stated in the last sentence are not fulfilled in the pedigree. The theory is rejected.

2. Carried on the nonhomologous segment of the X chromosome as a dominant, it may affect either sex. All the female children and none of the male of an affected male will show the trait. It may appear equally in male and female offspring of an affected female. Neither of these criteria is observed in this pedigree and the theory is rejected.

3. Carried on the nonhomologous segment of the X chromosome as a recessive, it affects only males in most families. It is transmitted to them by their unaffected mothers. This is observed to be true in this pedigree. But in this type of inheritance the trait is never transmitted from father to son; if the mother is a carrier, an affected father may have an affected son who nevertheless inherits the trait from his mother, not his father. In such cases, affected daughters should also appear but here they do not. If a rare trait appears in many collateral lines, as it does in this family, it will do so only if the males have married cousins, which is not true here. It is most improbable that each male who has an affected son should have married a carrier who is not related to him. Therefore, this theory is discarded.

B. Partial sex linkage in which the gene is carried on the homologous segments of the sex chromosomes involves inheritance from both parents in the case of a recessive gene; this would necessitate matings between cousins, if such a large number of matings between carriers or between affected and carriers are to be made. This is not supported by the evidence. If it is a partially sex-linked dominant, it should involve both sexes, appearing more often in female offspring of affected fathers than in male offspring, although there should be a certain percentage of males showing the trait due to crossing over. Again this is not supported by the pedigree and the theory is rejected.

C. Sex limited. In this mode of inheritance, the gene is not located on the sex chromosome, nor need it affect an organ limited to one sex. The trait is merely limited to one sex in its manifestations. It may be transmitted by persons of the opposite sex who cannot manifest it. This is true in this pedigree. The theory may be tentatively accepted that the trait is sex limited.

D. Sex influenced. In this mode of inheritance the heterozygous persons of one sex manifest the trait. On the other hand, only the homozygous persons of the other sex manifest the trait. If the trait is very rare, so that it is practically never present in the homozygous state, the sex-influenced trait is indistinguishable from the sex-limited, being present only in the sex which exhibits the trait in the heterozygote. Indeed, it is possible that they are expressions of the same mode of inheritance, sex limitation being its manifestations when the gene is rare, sex-influenced when the gene is common. There are no affected females and no opportunity for homozygous females to appear in this family. So that we cannot say whether they could appear if an affected male were to marry a carrier female and produce female offspring.

E. Recessive autosomal inheritance. This requires that both parents carry the gene in at least heterozygous form. If the trait is to occur in as many collateral lines as it does in this pedigree, and if it is also rare, it means either that each affected man who has affected children has married a carrier who is not related or he has married a carrier who is re-

lated. The latter is not true, and the former is a very remote probability. We therefore discard this theory.

F. Dominant autosomal inheritance. This requires that each affected offspring should have at least one affected parent, and that approximately half the offspring of each affected parent have the defect. It requires both sexes to be affected. These criteria are not exemplified in this pedigree. On the other hand, if the trait is rare and is found through as many

TABLE A

TABLE SHOWING NUMBER OF AFFECTED INDIVIDUALS OBSERVED AND EXPECTED, AMONG MALES ONLY—ASSUMING THAT TRAIT IS DOMINANT

No. in Family	No. in Families	No. of Males Affected Observed	No. of Males Expected to be Affected	(Standard Deviation)^2
1	6	6	6.	0.0000
2	8	10	10.664	1.7776
3	4	5	6.860	1.9592
4	1	1	2.134	.7822
5	2	5	5.162	2.1640
Total	21	27	30.820	6.6830

The difference between the expected and observed value is 3.82 which is almost 1.5 times the standard deviation $\sqrt{6.683}$ or 2.6.

Such a result is well in accord with the hypothesis that the trait is behaving as a dominant, affecting half the male offspring.

But in 2 instances unaffected males passed on the trait, showing that they had inherited the gene, although not expressing the effects. If these 2 be added to the 27 above, the difference between 30.820 and 29 is 1.82 or only about $\frac{2}{3}$ of the standard deviation.

as three consecutive generations, the evidence is rather good that it is dependent upon a dominant gene. That is sustained by this pedigree. Putting together the theories which we may accept, we have that,

1. It is sex limited, explaining its appearance only in the males, and its transmission to male offspring of normal females.

2. It is dominant, since it is found transmitted through four generations of males in one instance and through three generations in another. It is transmitted through females in whom it cannot become manifest in numerous other instances, acting as a dominant when it comes to a line of males.

3. There are two instances in which unaffected males transmitted it, thus suggesting that it is not fully penetrant, that is, it is not manifest in all those persons whose genetic makeup entitles them to exhibit the trait. We conclude then that it is a sex-limited autosomal dominant, not completely penetrant.

How does this theory agree with the observed facts? If the trait is dominant it should express itself in approximately half the males in a family in which it appears. In table A are set forth the observed and expected values, together with the standard deviations. There was a total of 27 males affected and the number expected in these families was 30.82. The difference was about 1.5 times the standard deviation, and the hypothesis that the trait is dependent upon a dominant gene is in accord with the observed data. But in two instances, males who are unaffected passed on the trait, as evidenced by the fact that

their sons were affected. If we add these two to the total of 27, we have a good fit between the observed and expected values. That only 27 of the 29 males whom we know inherited the gene actually expressed it phenotypically indicates a degree of penetrance of about 93%.

If the hypothesis is true that the gene is sex limited, but a dominant, then we should expect that about half of the females whose fathers or brothers have the trait should be able to pass it on to half their sons; also that the gene might descend unexpressed through several generations of females before being manifested in a male. We find 32 females who

TABLE B

TABLE SHOWING NUMBER OF AFFECTED CHILDREN OBSERVED AND EXPECTED, IN THOSE FAMILIES—ASSUMING THAT TRAIT IS DOMINANT

No. in Family	No. of Families	No. of Affected or Carriers Observed	No. of Affected or Carriers Expected	(Standard Deviation)^2
1	1	1	1	0.0000
2	6	8	7.998	1.3332
3	7	8	12.005	3.4286
4	3	3	6.402	2.3466
5	1	1	2.581	1.0820
6	2	5	6.094	2.7580
7	2	9	7.054	3.3340
8	1	4	4.015	1.9450
Total	23	39	47.149	16.2274

The difference between the expected number and the observed is more than twice the standard deviation, and would not be likely to arise by chance alone.

$47.149-39=8.149$ which is more than twice $\sqrt{16.2274}$ or 4.03.

had affected fathers, and only 9 of them passed on the trait. This would seem to be against the theory of dominance not able to express itself in the female because of sex limitation. On the other hand, a female who has inherited the gene can be identified only if she has affected sons or grandsons. If we inspect the pedigree again, we find that there were only 16 females whose fathers or brothers were affected that had sons by which they might be tested. Of these, nine proved to have transmitted it, an excellent approximation to one half. In the second generation a female with an unaffected mother, four affected brothers, and a sister with an affected son, had two children, a male and female. The male was unaffected, and when the pedigree was first collected would have been placed in the category of a female who might have inherited the gene, but did not. However, her daughter has just had an affected son, placing this woman in the category of a transmitter. It also gives the first instance in the pedigree of a female transmitter who had neither a father nor a brother affected.

If we arrange all the children male and female in a table B, we find that there are too few affected for the expected value of 47.149. The difference is a little more than twice the standard deviation. But remembering that females can be judged only if they have had sons by which their carrying the gene can be tested, we can rearrange the data as in table C omitting all those females who have not reproduced, or who have had only daughters.

TABLE C

TABLE SHOWING NUMBER OF AFFECTED CHILDREN OBSERVED AND EXPECTED, WHEN ONLY THOSE FEMALES WHO HAVE PRODUCED MALES ARE INCLUDED AMONG CARRIERS AND NORMAL—ASSUMING THAT TRAIT IS DOMINANT

No. in Family	No. of Families	No. of Affected or Carriers Observed	No. of Affected or Carriers Expected	(Standard Deviation)^2
1	6	6	6	0.0000
2	6	8	7.998	1.3332
3	6	7	10.290	2.9388
4	1	1	2.134	.7822
6	2	8	6.094	2.7580
7	2	9	7.054	3.3340
Total	23	39	39.570	11.1462

The difference between the observed and expected values is only about $\frac{1}{8}$ of the standard deviation, showing that there is very little deviation from the expected value as can be shown by the totals, 39. and 39.57.

In this table, those females who are in families with an affected brother or father are not counted unless they have produced a male. If they have not had offspring, or only female offspring, there is no way of knowing what their potentialities are. If they have produced normal males they are regarded as normal females, and are counted in the total children in the family: and of course they are counted if they have produced affected males.

TABLE D

TABLE SHOWING NUMBERS OF AFFECTED INDIVIDUALS, EXPECTED AND OBSERVED, AMONG CHILDREN OF CARRIER FEMALES

No. in Family	No. of Families	No. of Affected Males and Carrier Females Observed	No. of Affected Males and Carrier Females Expected	(Standard Deviation)^2
1	6	6	6	0.0000
2	2	2	2.666	.4444
3	1	1	1.715	.4898
5	1	4	2.581	1.0820
Total	10	13	12.962	2.0162

There is almost perfect agreement between the number of affected males and carrier females observed and expected. All females not producing a male were excluded, since they could not be tested for carrying the gene.

The difference is only about 1/37 of the standard deviation, 1.41.

When that is done, the observed and expected values are in almost perfect agreement.

It might be thought that carrier females do not transmit it as frequently as do the males who have it in the manifest form. If we look at the number of times that a female has transmitted, we find that 10 times a female has been able to transmit the gene. In those 10 families, 19 children were produced who could either show the trait itself, or who produced males who could show the trait. In 13 of the 19 possible affected children, the trait had been passed on, showing that the female passes it on as often as does the male. Thirteen of 19 times seems like far too high an incidence, when only half the children are expected to be affected. However, reference to table D shows that this is in almost perfect agreement with expectation. Since we can only tell that a female is a carrier by her having produced affected offspring or grandchildren, the data are weighted heavily in favor of affected children.

Conclusion

The trait in this family is dependent upon a sex-limited autosomal gene, showing a little less than complete penetrance (about 93%). It is transmitted by affected males, carrier females and the genotypically affected but phenotypically normal males to about half their offspring, irrespective of whether the parent manifests the trait or not. It is passed on to half the females who then may transmit it to their sons or to their daughters as carriers. In one instance it went through at least three generations of unaffected females to appear in an affected male.

Discussion

As compared with other mammals the human animal is unique in the relatively enormous length of the juvenile growth period during which sexual development is virtually at a standstill. Sexual maturation does not begin until physiologic maturation of the hypothalamic area of the mid-brain permits the issuing of impulses from this center which stimulate the anterior lobe of the pituitary to secrete gonadotropic and other hormones. Only by means of pituitary gonadotropins can the gonads be activated to full function. During immaturity this mechanism is presumably inhibited, and at puberty is finally released by the commencement of function of the neural center.[6-8]

In the course of the long childhood period there are many, astonishingly diverse, pathologic conditions which seem to be able to remove prematurely the normally-existing inhibitory effect on the neurohumoral mechanism responsible for sexual growth, thus bringing about precocious sexual development. By this is meant genital development which approaches adult proportions during the first 8 or 10 years of life; this maturation may proceed further to precocious puberty which is manifested by spermatogenesis or ovulation. A list of abnormalities which have been reported as associated with or responsible for premature sexual development would include:

Basophile adenoma of the anterior lobe of the pituitary
Hyaline degeneration of the basophile cells of the anterior lobe of the pituitary
Tumors of the anterior lobe of the pituitary
Tumors of the hypothalamus
Tumors of the cerebellum
Tuberous sclerosis
Hamartoma of the tuber cinereum
Tumors of the adrenal cortex

Hyperplasia of the adrenal cortex
Fuchsinophilic granules of the cells of the adrenal cortex
Granulosa cell tumors of the ovary
Arrhenoblastoma of the ovary
Multiple corpus luteum cysts of the ovary
Tumors of the testes
Tumors of the pineal body
Tumors of the thymus
Myxosarcoma of the prostate
Presacral teratoma
Osteodystrophia fibrosa in girls (Albright's disease)
Morgagni-Morel syndrome (osteitis frontalia interna)
Achondroplastic dwarfism
Familial cretinism
Insulin injections

All these heterogeneous pathologic conditions may produce some form of sexual precocity, and it seems not unlikely that in some manner through either an endocrine or neural route each is able to stimulate the pituitary.

In addition to cases in which the above defects are found there is a group in which no abnormalities are present other than the early development. They are essentially normal individuals in whom the long juvenile period is cut short by the abnormally early occurrence of normal puberty. These may properly be classed in a "primary constitutional" group. They have what has been designated as the "complete" type of sexual precocity due to early activation of a normal pituitary-gonadal mechanism, as compared to the "incomplete" type without maturation of the gonads but with development of secondary sex characters due to secretion of hormones by a gonadal or adrenal neoplasm. In the latter case the testes are small or atrophic, whereas in the "complete" type they are of adult size and normal consistency.

There is both clinical and experimental evidence to suggest that the tuber cinereum is an activating center of sexual behavior and it is thought by some that all constitutional precocity occurring in males is due to a congenital anomaly or hamartoma of the tuber cinereum. In fact Bronstein et al.[9] in commenting on Rush's original report (on a branch of the family reported here) assume without discussion that all his cases were in fact due to such an anomaly. While the presence of such a condition in 27 otherwise healthy individuals in one family group would seem unlikely, it must be admitted that it is within the realm of possibility.

The low values for urinary gonadotropins are rather surprising in the light of our present ideas regarding the mechanism of sexual development. There seems no reason to doubt the accuracy of the titrations, as others have made similar findings. Possibly the extreme sensitivity of young children to untimely stimulation by sex hormones allows apparently small increases above normal to induce maximal response. Wilkins[10] comments that "one would theoretically expect to find urinary gonadotropins in such a case. I have been able to demonstrate these in a few of my cases, but it is true that many have given negative results as in your patient. I do not know whether this means that the test is just not sensitive enough to pick up low levels or whether in the male cases luteinizing hormone alone and not follicle stimulating hormone is present."

The low 17-ketosteroid excretion is not surprising as in normal males this often ranges low well into puberty.[11,12]

Except for the cases described by Stone[1] (father and son), Orel[2] (two brothers), Sigrist[4] (two brothers) and Engstrom and Munson[5] (father and two sons), no other examples of multiple familial inheritance of this condition have been reported. The cases reported by Rush et al.[3] are members of the family described in this paper and are included in the pedigree as indicated on the chart.

A personal communication from Hugh R. Jolly, Great Ormond Street Hospital, London, says that he knows of the case of a father and son affected (unpublished).

It would seem fair to assume that males exhibiting this character develop it as the result of an altered endocrine balance induced by the presence of the dominant gene. The gene would seem to be one which causes overactivity of the anterior lobe of the pituitary in infancy and childhood, thus precociously stimulating both body growth and the endocrine function of the testes. The trait may fail to appear in the female who carries the gene either (1) because the gene fails to exert the same influence upon the anterior lobe due to genetic differences between the two sexes or (2) because the tendency toward overactivity of the anterior lobe stimulated by the gene is checked by an inhibitory influence of some other part of the endocrine balance is such that the hormones of the anterior lobe are kept below the threshold level required to induce the precocity. It is also possible that what is inherited may be an abnormal responsiveness to a normal amount of anterior lobe hormone.

Summary

A family is reported in which 27 males were affected with precocious somatic and sexual development.

The trait is shown to be dependent upon a sex-limited autosomal gene with a little less than complete penetrance.

Acknowledgment

Acknowledgment is made to Drs. H. P. Rush, J. B. Bilderbach, D. Slocum and A. Rogers for permission to include a summary of cases reported by them, and for assistance in tracing members of this family; also to Dr. C. Kelly Canelo and Dr. Morris L. Bridgeman for reports of patients under their care; and to Dr. Fuller Albright for laboratory tests.

References

1. Stone, R. K., Extraordinary precocity in development of male sexual organs and muscular system of child four years old, Am. J. M. Sc. **24**:561, 1852.
2. Orel, J., Kleine Beitrage zur Vererbungswissenschaft, Ztschr. f. d. ges. Anat. **13**:691, 1928.
3. Rush, H. P., Bilderbach, J. B., Slocum, D., and Rogers, A., Pubertas praecox (macrogenitosomia), Endocrinology **21**:404, 1937.
4. Sigrist, V. E., Über drei Fälle von genuiner und Einen Fall von zerebraler Pubertas praecox, Ann. paediat. **155**:84, 1940.
5. Engstrom, W. W., and Munson, P. L., Precocious sexual and somatic development in boys due to constitutional and endocrine factors, Am. J. Dis. Child. **81**:179, 1951.
6. Clark, W. E. L., Beattie, J., Riddoch, G., and Dott, N. M., Hypothalamus: Morphological, functional, clinical and surgical aspects, London, Oliver & Boyd, 1938.
7. Weinberger, L. M., and Grant, F. C., Precocious puberty and tumors of hypothalamus: Report of case and review of literature with pathophysiologic explanation of precocious sexual syndrome, Arch. Int. Med. **67**:762, 1941.

8. Bustamente, M., Experimentelle Untersuchungen über die Leistungen des Hypothalamus, besonders bezüglich der Geschlechtsreifung, Arch. f. Psychiat. **115**:419, 1942.
9. Bronstein, I. P., Luhan, J. A., and Mavrelis, W. B., Precocious puberty associated with hyperplastic abnormality of tuber cinereum, Deutsche med. Wchnschr. **64**:211, 1942; correction, ibid. **64**:723, 1942.
10. Wilkins, L., Personal communication to the authors.
11. Nathanson, I. T., and Aub, J. C., Excretion of sex hormones in abnormalities of puberty, J. Clin. Endocrinology **3**:321, 1943.
12. Wilkins, L., Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence, Springfield, Ill., Charles C Thomas, Publisher, 1950, p. 158.

SPANISH ABSTRACT

Precocidad Sexual Hereditaria; Reporte de una familia con 27 miembros afectados

El estudio de estos autores reporta una familia en la cual 27 individuos del sexo masculino presentaron un desarrollo somático y sexual precoz.

Este rasgo hereditario que es bastante raro lo tuvieron exclusivamente los varones, no causó muerte temprana en ninguno de ellos y la mayor parte de los individuos afectados vivieron hasta la madurez de la vida; eran personas normales con excepción de que tenían tendencia a ser cortos de estatura. No hubo consanguinidad en los matrimonios. En el estudio del árbol genealógico de la familia encontraron que dicho rasgo es trasmitido aproximadamente a la mitad de los descendientes por los varones afectados, las mujeres portadoras y por los hombres cuyo geno-tipo esta afectado pero con feno-tipo normal, ya sea que presenten o nó dicha característica. Igualmente este rasgo pasó a la mitad de las mujeres las cuales pueden trasmitirlo a sus hijos o a sus hijas transformándolas así en portadoras. En un caso esta característica pasó a traves de tres generaciones de mujeres normales antes de que hubiera un varón con dicho rasgo.

Revisando las teorias de la herencia que pudieran explicar como fué transmitido este carácter en concordancia con la genealogia de la familia encontraron que está limitada por el sexo lo cual explica su aparición exclusivamente en los varones y su transmisión a los hijos por mujeres normales; que se hereda como caracter dominante ya que se transmitió a través de 4 generaciones en un caso y tres en otro, que lo transmitieron las mujeres en las cuales no pudo manifestarse en numerosos ejemplos, actuando como dominante cuando nacían varones y finalmente, que no parece tener una penetración completa dado que dos individuos masculinos de la familia que por sus antecedentes genéticos debían haber sido afectados, no lo fueron, pero si lo transmitieron. Por estas consideraciones aceptan que esta caracterítica depende de un gene autosomático, limitado por el sexo, con penetración casi completa.

Se acepta en la actualidad que el mecanismo de la maduración sexual se inicia cuando se ha obtenido la maduración fisiológica del área hipotalámica, época en la cual se establece la salida de impulsos de este centro que estimularían el lóbulo anterior de la pituitaria, el cual secretaría las hormonas gonadotrópicas y otras de naturaleza distinta, siendo las primeras las que activarán las gónadas en forma funcional total. Se presume que durante el largo período de inmadurez previo a la pubertad dicho mecanismo se encuentra inhibido y que al iniciarse ésta, entra en funcionamiento dicho centro nervioso.

La etiología de esta característica es muy diversa. Se citan distintos tipos de tumores del lóbulo anterior de la hipófisis como el adenoma basófilo, del hipotálamos, cerebelo, de la corteza suprarrenal, del ovario, testículos, hamartoma del tuber cinereum, etc. la degeneración hialina de las células basófilas del lóbulo anterior de la pituitaria, hiperplasia de la corteza suprarrenal, etc. etc.

Dichas entidades patológicas serían capaces de liberar prematuramente el mecanismo normal de inhibición del sistema neuro-humoral responsable del crecimiento sexual acarreando consigo el desarrollo sexual precoz con las características del adulto aun cuando el varón no pase de los ocho o diez años de edad y aun continuar hasta desarrollar una pubertad precoz que se manifiesta por espermatogénesis o menstruaciones. Además de las causas arriba citadas hay otro grupo de casos en el cual no se presentan anormalidades que pudieran determinar el síndrome de desarrollo sexual precoz; son individuos prácticamente normales en los que simplemente el largo período juvenil fué recortado por el principio temprano de una pubertad normal.

Hay pruebas clínicas y experimentales que efectivamente sugieren la posibilidad de que el tuber cinereum es el centro activador de la conducta sexual y hay autores que piensan que toda precocidad constitucional que ocurra en los varones es debida a una anomalía congénita o hamartoma del tuber cinereum. Esta posibilidad es factible en los 27 miembros aquí reportados que por otra parte eran individuos sanos, pero improbable.

Es difícil explicar los valores bajos de las gonadotropinas urinarias en vista de las ideas presentes con respecto al mecanismo del desarrollo sexual. Posiblemente la sensibilidad extrema del niño al estímulo temprano de las hormonas sexuales permita que pequeñas cantidades arriba de lo normal determinen una respuesta máxima. No sucede lo mismo con la excreción de los 17 ketosteroides ya que si estos están bajos se observan niveles similares frecuentemente en varones normales cuando la pubertad esta ya bien avanzada.

La limitación de esta característica al sexo masculino podría explicarse asumiendo que los varones que la presentan la desarrollan como resultado de un trastorno del equilibrio endócrino inducido por la presencia de un gene dominante el cual provocaría la sobre actividad del lóbulo anterior de la pituitaria estimulando precozmente tanto el crecimiento del cuerpo como la función endócrina de los testículos. Esta característica no aparecería en la mujer que llevaría el gene, bien porque éste no fuera capaz de ejercer la misma influencia sobre el lóbulo anterior debido a diferencias genéticas existentes en los dos sexos o porque la tendencia hacia la sobreactividad del lóbulo anterior estimulado por dicho gene sea suprimida por una influencia inhibidora dependiente del equilibrio endócrino en tal forma que las hormonas del lóbulo anterior permanezcan debajo del umbral requerido para inducir la precocidad sexual. Por otra parte, también es posible que lo que se hereda sea mas bien la facultad de desarrollar una respuesta o reacción anormal a una cantidad normal de hormona del lóbulo anterior de la hipófisis.

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CONGENITAL ABSENCE OF THE SPLEEN; SYNDROME WITH ATRIOVENTRICULARIS AND SITUS INVERSUS

Case Reports and Review of the Literature

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CONGENITAL absence of the spleen has been reported seven times in the United States, and 15 cases have been reported elsewhere. Although the isolated condition is asymptomatic, the authors' observations have revealed the frequent association of a specific group of anomalies; namely, persistent atrioventricularis communis, partial situs inversus, accessory lobe of the left lung, and abnormal mesenteric attachments.

Absence of the spleen as well as of other major organs in nonviable monsters has been recorded since 1564;[1-3] that type of material, however, is not considered in the present report. This paper, therefore, proposes to review the literature dealing with absence of the spleen and to present detailed clinical and pathologic data from four additional cases seen in this clinic.

REVIEW OF LITERATURE

Incorrectly included by several authors with true cases were those reported by Patellani and Moroni[4] and Albrecht.[5] The former report dealt with an experimentally splenectomized dog and the latter with a case of multiple accessory spleens.

A total of 12 adult cases have been reported,[6-18] including several which may represent splenic abscesses rather than true ageneses. What appeared to be a localized collection of pus at the site of the spleen was found in the cases of both Libby[9] and Ramsey,[10] and tuberculous destruction of the spleen may have occurred in the cases of Sternberg[11] and Glinski.[12]

Although the adults with congenital absence of the spleen seldom have other anomalies, Charache's[18] case, in a patient who died of lymphosarcomatosis, is of interest because of transposition of the upper abdominal viscera.

In contrast to the findings in adults, most cases occurring in infants have had associated anomalies. The first established infantile case was that of Martin[19] in 1826. Autopsy revealed absence of the spleen, a right-sided stomach with part of the duodenum on the left, the liver divided into two equal parts, a transposed pulmonary artery and aorta, right and left superior venae cavae, an interauricular defect and a single ventricular cavity.

The next infantile case was that of Robert[20] in 1842. There was a rudimentary forearm and hand, arrested development of the stomach, and absence of the spleen and omentum. Arnold[21] described a 15 week old infant with a cor triloculare biatriatum, interauricular defect, communication of the pulmonary vein with the cystic vein and absence of the spleen, as well as anomalies of the portal vein, ductus venosus, hepatic vein and both venae cavae. There was also atresia of the pulmonary artery, a right-sided aorta, and a

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three-lobed left lung. Birch-Hirschfeld[22] discussed a newborn infant with no spleen or splenic vessels and a large asymmetric liver. By 1896 textbooks of pathology and medicine began to mention congenital absence of the spleen, its rarity, and its frequent association with other anomalies.[23-29]

McLean and Craig[30] reported a case in 1922 and presented an excellent review of the literature to that time. Their case was that of a 3 month old male with no spleen or supernumerary spleens. Additional anomalies included open auricular and upper ventricular septa, transposition of the great veins so that the venae cavae emptied into the left auricle and pulmonary veins into the right, three lobes of the left lung, four lobes of the right lung with an incomplete fifth lobe, and transposition of the right and left lobes of the liver. Hu[31] reported a case of a 7 month old male with the abdominal organs in mirror image position, the abdominal aorta on the right, the inferior vena cava on the left, and two superior venae cavae, one to each auricle. The mesenteric lymph nodes were enlarged. There was a small pulmonary artery which was transposed with the aorta, and an incomplete interauricular septum with an auriculoventricular opening which had a bicuspid valve. A single-chambered ventricle was present and the pulmonary veins connected to the gastric vein. The left lung had three lobes, the pancreatic duct opened separately into the duodenum, and the spleen was absent. Peterman's case[32] occurred in an 8 month old male with absence of the spleen, as well as of the left kidney and ureter, splenic artery and renal artery. The right ureter had a kink at the pelvic border with proximal dilatation.

Nelson and Venable[33] reported a case in a 14 month old male, who had "amniotic fluid pneumonia" as a newborn and later died of acute bacterial endocarditis and arterial thrombosis with gangrene of the left leg. Chronic pneumonia with fibrous tissue obliterating many pulmonary alveoli was found. There was no cardiac anomaly and the spleen and splenic artery were absent. Durie and Wyndham[34] reported two cases in 1942. The first was that of a 2 day old female with a right descending aorta, pulmonary artery atresia, two superior venae cavae, one to each auricle, and atrioventricularis communis. There was no spleen. The pancreas and duodenum were mobile, the greater omentum was absent and the stomach and intestines were in an abnormal position due to the abnormal mesentery. The second case was that of a one month old male. There was partial transposition of the heart and great vessels, the dorsal and ventral endocardial cushions were not fused, hence no division of the auriculoventricular channel existed. There was a defect of the dorsal mesogastrium. The greater omentum was absent. The pancreas lay on the gastric mesentery. The duodenum was mobile and the ileocecal junction lay in the iliac fossa. No spleen was found. Colome[35] reported a case of amniotic pneumonia with congenital absence of the spleen and situs inversus partialis. One of the cases described by Conn, Clark and Kissane[36] was a 3 year old male with a two-chambered heart, transposition of the abdominal viscera, and no splenic tissue. The auricular part of the heart was a single chamber which communicated with a single ventricle through fused mitral and tricuspid valves.

Four cases of absent spleen with associated anomalies have been autopsied in the space of two years at Children's Hospital. These bring the total number of established cases in infants to 16.

Case Reports

Case 1. R.S., a white male was born after an uneventful delivery and appeared normal at the time of birth. He was the seventh child in a family in which the other 6 children are living and

well. The mother recalled that she had had a severe attack of "old fashioned flu" during the first month of this pregnancy but was well otherwise. Two days after birth the infant's skin appeared rather dusky, and the attending physician heard a heart murmur. A few weeks later there was moderate generalized cyanosis and a systolic murmur was heard in the second and third left interspaces, transmitted to the left infraclavicular region. Fluoroscopy revealed no abnormalities of the lungs, but no pulmonary artery was seen. The heart was small and the pulmonary arch concave. The impression was tetralogy of Fallot.

During the next 18 mo. the child developed poorly. He was always cyanotic and had frequent spells of dyspnea and limpness. Numerous electrocardiograms were interpreted as follows: tall peaked P2; tall R in V3, AVR and AVL; deep S-waves in leads 1, 2, 3, AVF, V5 and V6; no

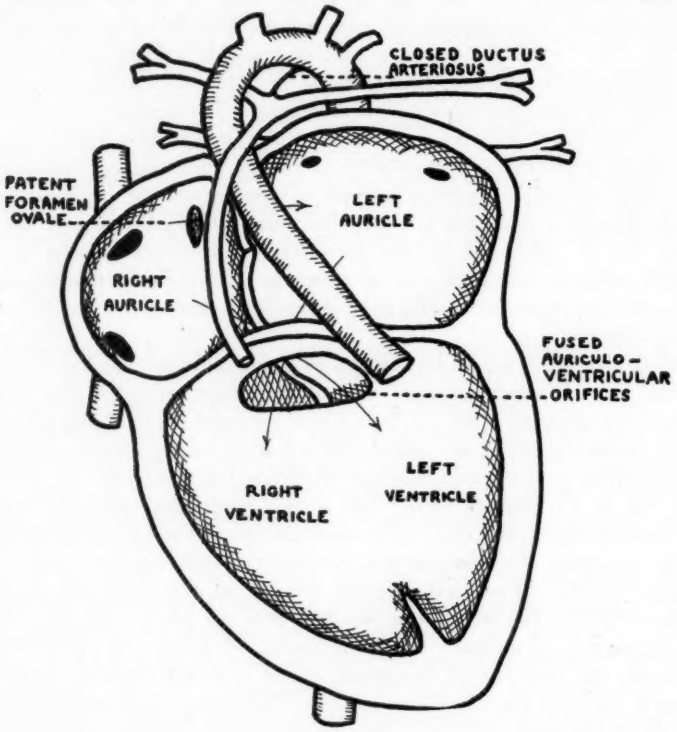

FIG. 1

axis deviation; right ventricular hypertrophy. Roentgenograms of the heart showed no cardiac enlargement; there was a concavity in the region of the pulmonary conus, a clear pulmonary window in the left anterior oblique and a right-sided aortic arch.

RBC count slowly rose from normal to 9 million/cmm. with Hgb. 25.4 gm./100 cc. at the time of the final hospital admission. The number of normoblasts in the peripheral blood was consistently high (up to 400/100 white blood cells), a finding which was never adequately explained even with the help of bone marrow studies and therapeutic trials of iron and folic acid.

At the age of 23 mo. the child was admitted to Children's Hospital for exploratory surgery. Operation was performed but no pulmonary artery could be found; hence no vascular anastomosis was performed. The child died 10 hr. after operation.

Autopsy: The body revealed fair development and good nutrition and measured 75 cm. in length (normal length stated for this age is 83 cm.). There was a recent thoracic surgical incision 30 cm. in length parallel to the left fourth rib. The nail beds were bluish-purple and there was

slight clubbing of the fingers. The peritoneum was thin and translucent, and the cavity contained about 5 cc. of clear fluid. There was 150 cc. free blood in the left pleural cavity and the left lung was partially collapsed. The right pleural cavity contained about 15 cc. of clear straw-colored fluid. The thymus was not remarkable. The heart (Fig. 1) appeared diffusely enlarged and with the lungs weighed 250 gm. (normal combined weight is 295 gm.). The right auricle was considerably enlarged and opened into the right ventricle. There was a ventricular septal defect measuring 2 x 2.5 cm. which made the ventricles appear as a single cavity. An interauricular septal defect measuring 1 cm. in diameter was also present inferior to a patent foramen ovale. The mitral and tricuspid valves were fused medially through the interventricular defect forming a single valve which measured 50 mm. in circumference. The aortic valve was 42 mm. in circumference. The pulmonary artery arose from the right ventricle and the lumen at the site of origin measured but 3 mm. in diameter. An irregular nodular mass constituted the pulmonic valve. The pulmonary veins returned to the left auricle, and the aorta arose from the left ventricle. The aorta was of normal caliber but descended on the right side. The innominate artery bifurcated 4 mm. from its origin. The ductus arteriosus was obliterated. The thickness of the left ventricular wall was 10 mm; the right ventricular wall 8 mm. The coronary ostia were in their usual locations, and the vessels were patent.

Both lungs had 3 lobes, and an incomplete fissure extended across the left lowest lobe. The left lung was somewhat compressed by the free blood in the pleural cavity. Both lungs were dark red externally and had little crepitus on palpation. The cut surfaces were of a dark red color, and a small amount of dark red fluid could be expressed.

The liver weighed 250 gm. (normal weight for this age, 387 gm.). It was reversed in shape, the caudate lobe lying to the right of the inferior vena cava and the larger mass of the liver substance lying on the left side. The external and cut surfaces were a dark red-brown color and the lobulations appeared normal. The gallbladder occupied a position on the inferior surface of the liver to the left of the midline. The cystic and common bile ducts entered the duodenum through the ampulla at the usual site. The pancreatic duct entered the duodenum separately, directly opposite the ampulla of Vater. No spleen was present, nor were there any splenunculi. No splenic vessels were found. The pancreas appeared somewhat larger than usual and weighed 20 gm. It was very mobile, and the tail lay inferiorly to the duodenum, which was normally situated. The jejunum was not remarkable, but the distal portion of the ileum and the entire colon was incompletely rotated, the cecum lying on the left side and the sigmoid colon on the right. The adrenals were normal as to position and gross structure.

The kidneys weighed 55 gm. each (normal weight for this age, 45 gm.), and showed slight fetal lobulation. The external and cut surfaces revealed no abnormalities, and the ureters were patent throughout. The testes were in the inguinal canals and exhibited their usual external and cut surfaces. There was slight inguinal and axillary lymphadenopathy. The brain was not remarkable.

Microscopic examination: The nuclei of the heart muscle fibers were enlarged, hyperchromic and barrel-shaped. In the lungs the capillaries of the alveolar walls were dilated and engorged with blood. A small thrombus with early organization was seen in one small pulmonary vein. A small artery showed intimal proliferation. There were small areas of atelectasis and emphysema. The trachea showed edema and marked vascular congestion of the submucosa. There were many areas of polymorphonuclear infiltration as well as lymphocytic and plasma cell infiltration in the tracheal submucosa, and the mucosa was necrotic and sloughed off in one area. The blood vessels of the kidneys including those in the glomerular tufts were all engorged, and there was marked hemorrhage in the interstitial tissue of the medulla. The thymus, liver, gallbladder, pancreas, gastrointestinal tract, adrenals, bladder, testes, aorta, pituitary and brain sections were all within normal limits, except for the presence of mild vascular congestion. The bone marrow showed marked erythropoiesis.

Final anatomic diagnosis: 1. congenital heart disease: a. persistent atrioventricularis communis, b. pulmonary stenosis, c. right aortic arch, d. cardiac hypertrophy; 2. partial situs inversus, liver, gallbladder and intestine; 3. tracheitis, acute, ulcerative; 4. congenital absence of the spleen; 5. hemothorax, left; 6. congestion, generalized; 7. anomalous left lobe, lung; 8. thrombosis, small, pulmonary vein; 9. elongated pancreatic mesentery.

Case 2. D. L., a white male, was born after a full-term normal delivery. He was the second child in the family, a sister, age 3 yr., being in good health. The mother was hospitalized during the fourth month of gestation because of pain in the lower abdomen. This, however, subsided. She also had severe backaches throughout her pregnancy. There were no known infections.

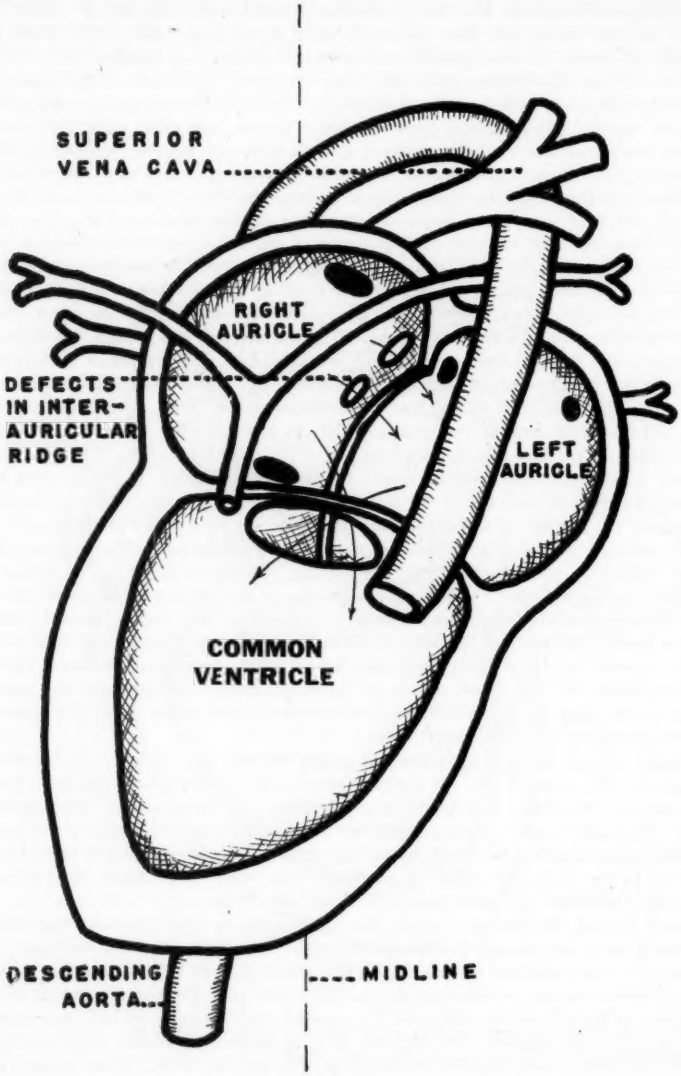

FIG. 2

The infant appeared normal at birth. At the age of 1 wk., after he had been discharged from the hospital, the parents noticed blueness of his skin. By the time he was 4 mo. of age, hospitalization had been necessary on 2 occasions because of respiratory distress. He was first examined in this clinic at the age of 4 mo. when it was found that he had a harsh systolic precordial murmur heard best in the fifth and sixth interspaces to the left of the sternum. The murmur was transmitted to the axilla. The liver was palpable 6 cm. below the right costal margin. The skin appeared cyanotic. It was believed that early clubbing of the fingers was present. There were no other abnormalities. The ECGs were interpreted as showing dextrocardia with right axis deviation, a vertical heart, and anterior

ventricular hypertrophy. Fluoroscopy of the heart revealed a dextrocardia with a concave pulmonary conus, minimal hilar markings and no hilar pulsations. A clear pulmonary window was seen in the right anterior oblique. The aortic arch was on the right. Hgb. was 12 gm. with RBC count 5.5 million/cmm. The WBC count was 13.3 thousand/cmm. with a normal differential. The urine studies were all within normal limits. A tentative diagnosis of dextrocardia with tetralogy of Fallot was made.

Cardiac surgery was considered advisable but deferred until a later date. The child, however, continued having repeated attacks of dyspnea and finally died at the age of 1 yr.

Autopsy: The body showed good development and nutrition, and measured 77 cm. in length (normal length for this age, 73 cm.). The nail beds were dark purplish in color, and a moderate amount of clubbing of the ends of the fingers was present. The peritoneum was thin and translucent, and there was no free peritoneal fluid. The lungs filled the pleural cavities, and each pleural cavity contained about 10 cc. of clear straw-colored fluid.

The heart (Fig. 2) appeared to be transposed in position, its larger portion lying to the right side of the midline. With the lungs, the heart weighed 216 gm. (normal combined weight 165 gm.). The superior vena cava emptied from the left side into a part of the right auricle which lay anteriorly in the midline. The rest of the right auricle lay on the right side. The major portion of the heart consisted of a large ventricle into which both auricles opened. Arising from the left side of this ventricle was the aorta which descended on the right side of the body. The pulmonary veins emptied into the left auricle, which lay posteriorly toward the left. This auricle opened into the right auricle through an interauricular septal defect measuring 2 cm. in diameter. Only a small ridge of tissue separated the 2 auricles and there were 2 small openings in this ridge. The auricles opened directly into the ventricular cavity through a large common valve which had 3 leaflets and apparently represented fused mitral and tricuspid valves. The pulmonary artery arose from the right side of the ventricle, its origin lying behind several papillary muscles. The vessel was quite small, its inside diameter being 3.5 mm. Only a rudimentary pulmonic valve was present. The aortic valve measured 3.5 cm. in circumference, and the fused mitral and tricuspid valve measured 6 cm. The common ventricular wall measured 9 mm. in thickness. The ductus arteriosus was occluded. The coronary ostia arose distal to the aortic valve and presented no anomalies.

Each lung had 3 lobes. They were pale red externally and were crepitant on palpation. On cut sections a mottled red color was seen, and a small amount of pinkish fluid could be expressed from the cut surface.

The liver weighed 243 gm. (normal weight 288 gm.). It was not transposed. The gallbladder and extrahepatic bile ducts presented no anomalies. No spleen was present nor were there any splenunculi. The pancreas was not remarkable; there was no abnormal lengthening of its mesenteric attachment. The cecum did not have its usual mesenteric attachment, but lay quite freely in the right lower quadrant. No other abnormalities of the intestinal tract were present. The adrenals were negative as to structure and position. The kidneys were not remarkable, nor were the ureters or bladder. Both testes were in the scrotum. The brain showed no abnormalities.

Microscopic examination: Some of the nuclei of the heart muscle fibers were enlarged and barrel-shaped. The capillaries of the lungs were quite congested. Organized thrombi were seen in several small pulmonary veins. Near the pleura in one section was a small wedge-shaped area of fibrosis and round cell infiltration. Many alveoli were filled with large mononuclear cells, some of which were filled with clear vacuoles. The remaining viscera all showed vascular congestion. In the kidney there appeared to be tiny interstitial hemorrhages in some areas of the cortex. A few hyalinized glomeruli were noted, and one showed capsular endothelial proliferation. The bone marrow was hyperplastic.

Final anatomic diagnosis: 1. congenital heart disease: a. persistent atrioventricularis communis, b. dextrocardia, c. pulmonary stenosis, d. cardiac hypertrophy; 2. congenital absence of the spleen; 3. elongated mesentery, cecal region; 4. accessory lobe of the left lung; 5. thromboses, organized, pulmonary vessels; 6. oil pneumonia, focal.

Case 3. G. B., a white female, was born after an uneventful pregnancy. Her only sibling died at 11 mo. with cyanotic congenital heart disease. (Autopsy on this sibling revealed a persistent atrioventricularis communis, multiple accessory spleens, partial transposition of the abdominal viscera, and a Meckel's diverticulum.) The child was believed normal at birth but became cyanotic soon thereafter. Her first admission to Children's Hospital was at the age of 8 days because of high fever. Physical examination revealed a listless, mildly cyanotic, dehydrated infant with a loud rasping sys-

tolic murmur heard over the entire precordium. It was believed that the baby suffered from sepsis; she was treated with antibiotics and the symptoms subsided. However, cultures failed to reveal the pathogen. Fluoroscopy of the chest showed a small heart with a concave pulmonary conus. The pulmonary window was clear via the left anterior oblique position, and posterior ventricular enlargement was also seen in this position. ECG was interpreted as showing intermediate heart position, posterior shift of the apex, and right ventricular hypertrophy.

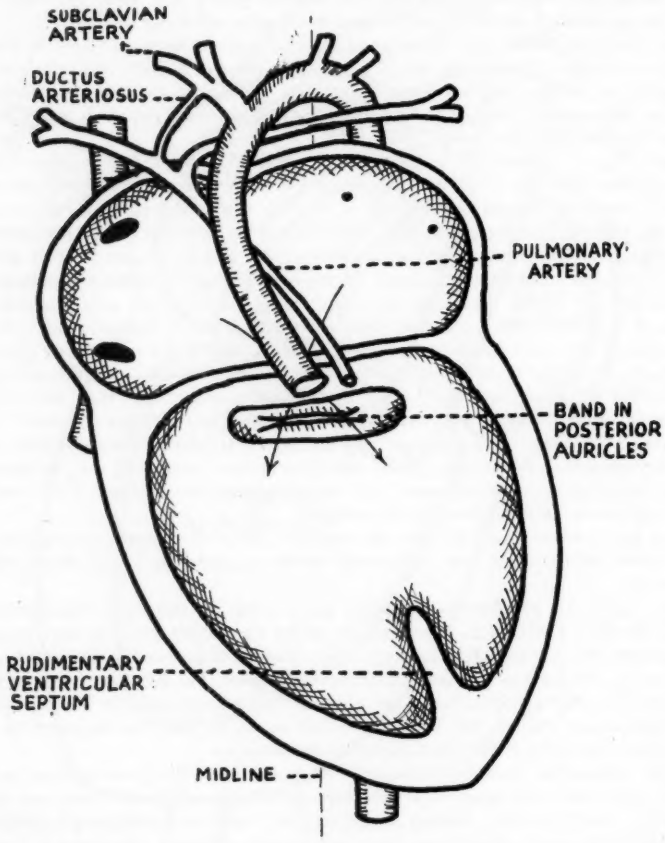

FIG. 3

The baby was followed as an outpatient for several weeks, but then readmitted because of dyspnea. Physical findings were unchanged except that the liver was felt 2 cm. below the right costal margin. Chest RG showed bronchopneumonia. Despite supportive therapy, the infant died.

Autopsy: The body appeared well developed and measured 51 cm. in length (normal for age 53 cm.). External examination was not remarkable except for cyanosis and poor skin turgor. The pleural and peritoneal cavities appeared normal with no free fluid, and the major viscera with the exception of the heart were in approximately their usual positions.

The heart, lungs and great vessels intact weighed 130 gm. (normal combined weight 81 gm.), and the cardiac apex was directed posteriorly toward the left (Fig. 3). The aorta lay directly anteriorly in its ascending portion. It was long, slightly tortuous, and descended on the left. A large patent ductus arteriosus joined the right subclavian artery with the right pulmonary artery at its bifurcation. There were no changes in the epicardium. The consistency of the myocardium was increased and the

papillary muscles were enlarged. Some thickening of the chordae tendineae was present. A single combined auricle was joined with a single ventricle through a fused mitral and tricuspid valve. This valve had 3 poorly defined cusps and measured 5.3 cm. in circumference. Posterior to this valve was a thin muscular band running transversely through the single auricle. The interventricular septum consisted only of a vertical ridge dividing the anterior third of the chamber. The aortic valve measured 3.7 cm. and had 3 slightly thickened cusps. The pulmonic valve was markedly stenotic. A 1 mm. probe could just be passed through the valve but immediately met with obstruction in the pulmonary artery. This artery arose in the ventricle to the left of the rudimentary septum; the aorta arose near the midline. The thickness of the ventricular wall was 6 mm. No abnormalities of the coronary arteries were present.

The right and left lungs had 3 distinct lobes and were mirror images. On section a few tiny patchy areas of yellow exudate were seen. The tracheobronchial lymph nodes were soft, reddish and enlarged.

The liver weighed 155 gm. (normal, 133 gm.). The left lobe was equal in size and similar in shape to the right lobe. The caudate lobe had its base confluent with the right lobe and was posterior to the duodenum and stomach. The gallbladder lay in the midline with the bile ducts directed posteriorly and slightly to the right. No splenic tissue was present. The pancreas was attached by a long, loose mesentery. The esophagus and stomach were not remarkable except for a slight displacement of the latter toward the left. The mesenteric attachment of the duodenum was very small. The jejunum and ileum were only partially rotated and the cecum lay free near the midline of the lower abdomen. A Meckel's diverticulum of the ileum was present 15 cm. from the cecum.

No abnormalities of the adrenals, kidneys, lymphatic system or musculoskeletal system were present. At the base of the brain was a moderate amount of creamy exudate. Smaller similar patches were noted on the superior surface of the temporal lobes and in the sulci of the motor and premotor areas. Small petechiae were also seen in these areas.

Microscopic examination: There was moderate hypertrophy and variation in size of the nuclei of cardiac fibers, some nuclei being quite large. The pulmonary vessels were engorged. Some alveoli contained pale pink-staining material. A dilated bronchus without inflammatory reaction was seen. Numerous polymorphonuclear leukocytes were noted in the peripituitary tissue. However, the remainder of the brain sections showed no such exudate. Sections of thymus, trachea, gastrointestinal tract, adrenals, kidneys, bladder, aorta and bone marrow were not remarkable. Meningeal culture yielded Staph. aureus hemolyticus.

Final anatomic diagnosis: 1. congenital heart disease: a. transposition of great vessels, b. persistent atrioventricularis communis, c. pulmonary stenosis and atresia, d. right ventricular hypertrophy, e. patent ductus arteriosus; 2. congenital absence of spleen; 3. pulmonary edema; 4. incomplete rotation of intestines; 5. supernumerary lobe, left lung; 6. Meckel's diverticulum; 7. malformed liver; 8. meningitis, focal, acute.

Case 4. R. J., a white male, was born after an uneventful pregnancy and delivery. He was the third child of the family, and the siblings were in excellent health. At birth no abnormalities were noted, but cyanosis of the hands and feet was observed on the second day of life. This persisted intermittently even though the baby was constantly in oxygen.

He was admitted to Children's Hospital at the age of 5 days. Examination revealed a well nourished and well developed infant who showed moderate generalized cyanosis. A soft systolic murmur was heard over the entire precordium. The liver was felt 2 cm. below the left costal margin, and the spleen tip was believed palpable. Except for white thrush-like lesions in the mouth and a foul umbilical discharge, the remainder of the physical examination was not remarkable. A blood count revealed: Hgb. 19.9 gm./100 cc.; WBC count 17.1 thousand/cmm. with 64% granulocytes, 33% lymphocytes and 3% monocytes; a Staph. aureus hemolyticus was isolated from the umbilical cord culture; blood culture negative. Chest fluoroscopy revealed no significant cardiac enlargement. There was marked concavity in the region of the pulmonary conus. The cardio-thoracic ratio was 5.5/9.6. Barium swallow showed the stomach to be on the right and the liver on the left. An ECG was interpreted as showing left axis deviation, horizontal heart, and possible left ventricular hypertrophy.

Despite supportive therapy and the use of antibiotics, the baby died after 5 days' hospitalization.

Autopsy: The body showed good development and nutrition and measured 51.5 cm. (normal for age 52 cm.). No free peritoneal or pleural fluid was present and the viscera were in their usual locations with the exception of the liver and stomach which appeared to be transposed. Moderate thymic enlargement was noted.

The heart (Fig. 4) weighed 23 gm. (normal for age 19 gm.). No visible lesions of the epicardium, myocardium or endocardium were present. The venae cavae emptied into the right side of a large auricle which was undivided except by a small ridge of tissue. A larger tissue ridge formed an incomplete septum of a combined ventricular cavity. The auricular and ventricular chambers were separated by a single valve which had 3 cusps and measured 5 cm. in circumference. Although the aorta arose from the left part of the ventricle and was normal in caliber, the pulmonary artery was completely atretic immediately distal to its origin. The ductus arteriosus was patent, though narrow, and joined with a small pulmonary artery. Coronary arteries arose from the 2 posterior aortic sinuses.

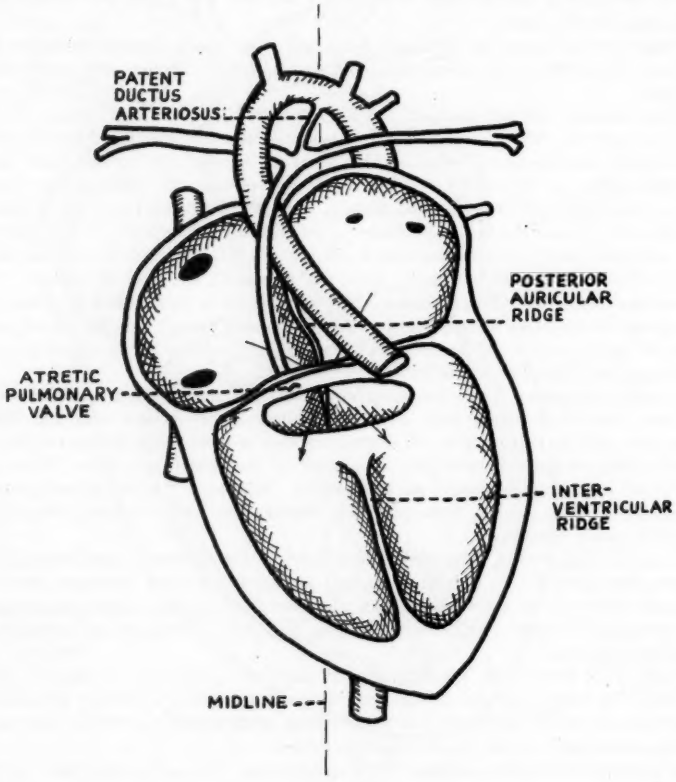

FIG. 4

Each lung had 3 distinct lobes. Small round flat red areas were scattered over the pleural surfaces. Crepitation was diminished throughout. Variable indistinct dark red areas were seen on cut section. The vessels seemed engorged.

The left lobe of the liver was distinctly larger than the right, causing the stomach to be shifted toward the right side. Both the caudate and quadrate lobes were incorporated in the left lobe. The gastric impression was visible on the right undersurface of the liver. The gallbladder also was on the right. Neither spleen nor splenic vessels were present. The pancreas appeared normal. Except for a high cecum and the displacement of the stomach, the gastrointestinal tract was unremarkable.

No abnormalities of the adrenals, kidneys, lymphatic system, musculoskeletal system or central nervous system were apparent.

Microscopic examination: Many of the heart muscle fibers were enlarged and exhibited broad nuclei. The lungs showed generalized vascular engorgement and most alveoli contained small

amounts of pink granular material. Hematopoiesis was prominent in the liver sinusoids. All viscera showed vascular congestion but otherwise were not remarkable.

Final anatomic diagnosis: 1. congenital heart disease: a. persistent atrioventricularis communis, b. atresia, pulmonary valve, c. stenosis, pulmonary artery, d. patent ductus arteriosus; 2. congenital absence of the spleen; 3. situs inversus, stomach; 4. situs inversus, liver, partial; 5. accessory lobe, left lung; 6. extramedullary hematopoiesis, liver; 7. passive congestion, viscera.

Discussion

Congenital absence of the spleen may occur alone or in association with other major anomalies. The former condition is compatible with a full life span; the oldest instance reported was found in a 73 year old woman.[11] Death in the adults has usually resulted from some disease involving the lymphatic system, i.e., tuberculosis, typhoid fever, malaria or lymphosarcoma (table 1). The fact that some of the patients listed in this report as having congenital absence of the spleen might actually have had their spleen destroyed by the disease which caused death would make the occurrence of isolated absence of the spleen more unusual and the incidence of cases associated with other anomalies relatively more common. All of this latter group who do have associated major anomalies apparently die in infancy.

The authors' survey of the literature in addition to the four cases reported here has revealed a definite syndromic occurrence of absent spleen, persistent atrioventricularis communis, accessory lobes of the lung, partial situs inversus of the abdominal viscera, and anomalies of major blood vessels in 13 of the 16 cases in infants. In most cases the cardiac defects were reported as cor triloculare biatriatum plus an interauricular defect. However, the descriptions and diagrams of those cases fit the picture of persistent atrioventricularis communis.

As is the case with most anomalies, the etiology remains obscure. Splenic primordia arise on the left side of the dorsal mesogastrium in embryos of 8 mm. (five weeks).[37] The major changes concerned with elaboration of septa and valves leading to the formation of a four-chambered heart, rotation of the gut, and formation of all the bronchial buds have not been completed at this age. No record of abnormalities of the maternal course during pregnancy appeared in any of the cases in the literature, but in the first case reported here, the mother gave a definite history of severe "old fashioned flu" during the first month of gestation. It is conceivable that some type of maternal illness prior to the fifth week of gestation when the embryo is less than 8 mm. in size might affect the embryo so as to produce any or all the anomalies discussed herein. However, the occurrence of almost identical anomalies in siblings born 18 months apart (Case 3) indicates that these anomalies are not a result of maternal illness during pregnancy, but are due to a basic defect in the germ plasm.

Summary

Four cases of congenital absence of the spleen are presented with a review of the literature. It is noted that this anomaly usually occurs as a syndrome with persistent atrioventricularis communis, partial situs inversus of the abdominal viscera, and accessory lobes of the lung.

Addendum

Since completion of this report a case of congenital heart disease, absent spleen and partial situs inversus was described by Sanford L. Leikin in the August 1951 issue, Clinical Proceedings of the Children's Hospital, Washington, D.C.

TABLE 1

Diseases Associated with Absence of Spleen

	Infantile Cases																Adult Cases									
Year	1826	1842	1868	1871	1922	1929	1932	1941	1942	1942	1945	1950	1951	1951	1951	1951	1845	1879	1896	1898	1903	1904	1906	1914	1918	1942
Author	Martin	Robert	Arnold	Birch-Hirschfeld	McLean and Craig	Hu	Peterman	Nelson and Venable	Durie and Wyndham	Durie and Wyndham	Colome	Conn et al.	Authors' case #1	Authors' case #2	Authors' case #3	Authors' case #4	Sachs	Koch and Wachsmuth	Olaechea	Hodenpyl	Sternburg	Kohlhass	Glinski	Riches	Rose	Charache
Patient's Sex	?	F	F	?	M	M	M	M	F	M	?	M	M	M	F	M	F	M	M	M	F	F	F	F	M	M
Patient's Age	6 w	3 d	4 m	1 h	3 m	7 m	8 m	14 m	2 d	1 m	?	3 y	23 m	12 m	6 w	10 d	47 y	49 y	?	32 y	73 y	54 y	45 y	45 y	56 y	49 y
Cardiovascular:																										
Atrioventricularis communis	+		+		+	+			+	+		+	+	+	+	+										
Dextrocardia																										
Pulm. sten. or atresia			+			+			+			+	+	+	+											
Rt. sided aorta			+			+			+			+	+	+	+											
Transp. gt. vessels	+									+		+														
2 sup. venae cavae	+					+			+																	
Anom. inf. vena cava			+									+														
Anom. pulm. veins			+		+	+			+						+											
Anom. of portal, hep. or cystic veins			+																			+				
Cerebral hemorrhage								+																		
Arterial thrombosis																										
Gastrointestinal:																										
Partial situs inversus	+			+	+	+			+	+	+	+	+		+	+										+
Transp. of stomach	+					+			+			+														
Maldevel. of stomach		+																								
Transp. intestines	+					+			+	+		+	+		+	+										+
Mesenteric anom.		+							+	+		+	+	+	+											
Transp. pancreas						+				+																
Anom. pancr. duct						+							+													
Transp. liver				+	+	+						+	+		+	+										+
Var. shape liver	+																					+				
Inguinal hernia																									+	
Accessory lobes of lung			+		+	+							+	+	+	+										
Absent kidney							+																			
Anomalous extremity		+																								
Other associated cond's.:																										
Meningitis															+											
Hydrocephalus												+														
Lymphadenopathy						+													+	+						+
Lymphosarcoma																								+		+
Typhoid																		+								
Malaria																			+	+	+		+			
Tuberculosis																										

References

1. Heusinger, C. F., cited in Hodenpyl, E., Case of apparent absence of spleen with general compensatory lymphatic hyperplasia, M. Rec. **54**:695, 1898.
2. Lemery, cited in McLean, S., and Craig, H. R., Congenital absence of spleen, Am. J. M. Sc. **164**:703, 1922.
3. Pohl, J. C., cited in McLean and Craig.[2]
4. Patellani, L., and Moroni, E., cited in Hodenpyl.[1]
5. Albrecht, H., cited in Sternberg, C., Ein Fall von Agnesie der Milz, Virchows Arch. (Berlin) **173**:571, 1903.
6. Sachs, J. J., cited in Hodenpyl.[1]
7. Jelenski, Fehlen der Milz, Berlin klin. Wchnschr. **17**:704, 1880.
8. Hodenpyl.[1]
9. Libby, R., cited in Hodenpyl.[1]
10. Ramsey, H. A., cited in Hodenpyl.[1]
11. Sternberg.[6]
12. Glinski, L. K., cited in McLean and Craig.[2]
13. Koch and Wachsmuth, Fehlen der Milz, Berlin klin. Wchnschr. **16**:81, 1879.
14. Olaechea, G. M., cited in Hodenpyl.[1]
15. Kohlhaas, cited in McLean and Craig.[2]
16. Riches, R. G., cited in McLean and Craig.[2]
17. Rose, F. G., Absence of spleen, Brit. M. J. **1**:591, 1918.
18. Charache, H., Lymphosarcomatosis and congenital absence of spleen, New York State J. Med. **42**:1363, 1942.
19. Martin, M. G., Observations d'une déviation organique de l'éstomac, d'une anomalie dans la situation, dans la configuration du coeur et des vaisseaux qui en partent ou qui s'y rendent, Bull. Soc. Anat. de Paris **1**:39, 1826.
20. Robert, H. L. F., Hemmungsbildung des Magens, Mangel der Milz und des Netzes, Arch. f. anat. Physiol. und Wissenschaftl. Med., 1842, p. 57.
21. Arnold, J., Ein Fall von cor triloculare biatriatum, Communication der Lungenvenen mit der Pfortader under Mangel der Milz, Virchow's Arch. f. path. Anat. **42**:449, 1868.
22. Birch-Hirschfeld, F. V., cited in Adami, J. G., and Nicholls, A. G., Principles of Pathology, Philadelphia, Lea & Febiger, 1929, vol. 2, p. 222.
23. Kaufman, E., Lehrbuch der speciellen pathologischen Anatomie, Berlin, George Reimer, 1904, p. 116.
24. Ribbert, H., cited in McLean and Craig.[2]
25. Stengel, A., cited in Hodenpyl.[1]
26. Ziegler, E., Textbook of Special Pathologic Anatomy, New York, Macmillan Company, 1896, p. 104.
27. Adami and Nicholls.[22]
28. Delafield, F., and Prudden, T. M., Textbook of Pathology, ed. 8, New York, William Wood & Company, 1907, p. 452.
29. Hektoen, L., and Riesman, D., American Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1901.
30. McLean and Craig.[2]
31. Hu, C. H., Absence of spleen, case with congenital malformation of heart with anomalous insertion of pulmonary veins, situs inversus of abdominal viscera, and other developmental errors, Am. J. Path. **5**:389, 1929.
32. Peterman, M. S., Congenital absence of spleen and left kidney, J.A.M.A. **99**:1252, 1932.
33. Nelson, R. L., and Venable, D. R., Congenital absence of spleen and chronic amniotic fluid pneumonia: Case, J. Lab. & Clin. Med. **26**:772, 1941.
34. Durie, B., and Wyndham, N. R., Description of two human specimens with congenital absence of spleen, abnormal arrangements of great vessels, abnormal cardiac cavities and other congenital defects, M. J. Australia **2**:174, 1942.
35. Colome, P. C., Amniotic pneumonia in case with congenital absence of spleen and situs inversus partialis, Rev. med.-quir. de Oriente **6**:22, 1945.

36. Conn, J. J., Clark, T. E., and Kissane, R. W., Cor biloculare, Am. J. Med. 8:180, 1950.
37. Arey, L. B., Developmental Anatomy, Philadelphia, W. B. Saunders Company, 1941, p. 356.

SPANISH ABSTRACT

Sindrome de Ausencia Congenita del Bazo con Atrioventricularis Comunis y Situs Inversus

Haciendo una revisión de la literatura los autores de este artículo encontraron 12 casos de niños con ausencia congénita del bazo que sumados a cuatro más estudiados por ellos hacen un total de 16 casos.

Contrariamente a los casos en adultos existía simultáneamente un grupo específico de anomalías, principalmente atrioventricularis comunis persistente, situs inversus parcial, lóbulo accesorio en el pulmón izquierdo, fijación anormal del mesenterio, que son las responsables de que estos niños mueran en la infancia; efectivamente, los casos reportados en adulto con excepción de uno, sólo tenían ausencia del bazo. Consecuentemente, es lógico aceptar la identidad de un verdadero síndrome cuya etiología es desconocida.

Es posible, afirman, que se trate de un defecto básico del plasma germinal como sugiere uno de los casos cuyo hermano nacido con 15 meses de diferencia presentó el mismo síndrome o por alguna enfermedad materna contraída antes de la quinta semana del embarazo, que lesione las estructuras embrionarias que posteriormente dan origen a los órganos afectados en este síndrome.

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ORTHODONTIC PROBLEMS IN PEDIATRIC PRACTICE

By T. M. GRABER, D.D.S., M.S.D., PH.D.
Chicago

ONE of the most important phases of oral health is the form and function of the oral mechanism. That specialty of dentistry which has as its goal the correction of dental malformations and restoration of the continuity and proper function of the teeth and jaws is called orthodontics. While parents have long been concerned with the obvious esthetic disabilities of malposed teeth, the pathologic implications of these malposed teeth have been the primary concern of the orthodontist. Frequently, tooth malpositions or dental malocclusions reflect growth and developmental disturbances of the upper and lower jaws. Crooked teeth are unsightly, but more important, they probably are functioning improperly, or not at all, which seriously impairs the health and longevity of the teeth and investing tissues.

Recent studies of facial growth indicate that dental malocclusions may be grouped in three morphologic categories, on the basis of jaw development and individual tooth malpositions. First, are those types of disturbances which are primarily skeletal in nature. These are problems where the maxilla or mandible has assumed an abnormal relationship to one another, usually through an upset in the timetable of normal development. The teeth in each dental arch may be normal in their position when compared to their respective jaws, but the abnormal jaw relationship means that the upper and lower teeth meet improperly during mastication, deglutition and speech. The second group consists of relatively local disturbances, with the teeth malposed, but with normal jaw relationship. The third group is a combination of the first two, with both improper jaw relationship and with teeth in abnormal positions. Within these three broad categories one may find all sorts of tooth malpositions and jaw relationships; the premaxillary segment may be displaced anteriorly, the whole lower dental arch may be retruded, the upper cuspids may be erupting in the palate, etc. Such conditions may be separate or occur in combination.

There is a striking similarity in certain types of dental malocclusions. Grouping types of disturbances on a morphologic and developmental basis is not precise enough, nor descriptive enough, to recognize the inherent pattern similarities and therapeutic implications. Within a broad range, the aims of orthodontic therapy are the same for many cases within a specific category. A number of attempts have been made to classify malocclusions so as to better systematize dento-facial deformities and therapy. The classification most universally used was developed some years ago by Angle.[1] He recognized that the first molar teeth were probably the most stable dental units. Also, he noted that, based on anteroposterior jaw relationship, he could divide malocclusions into three groups, each of which had a large number of similar characteristics. Class I consisted of all cases with normal cranio-facial development, with normal anteroposterior relationship of upper and lower teeth, but with local malpositions (Fig. 1). Class II consisted of all cases where the lower molars had assumed a posterior relationship to the upper molars, with

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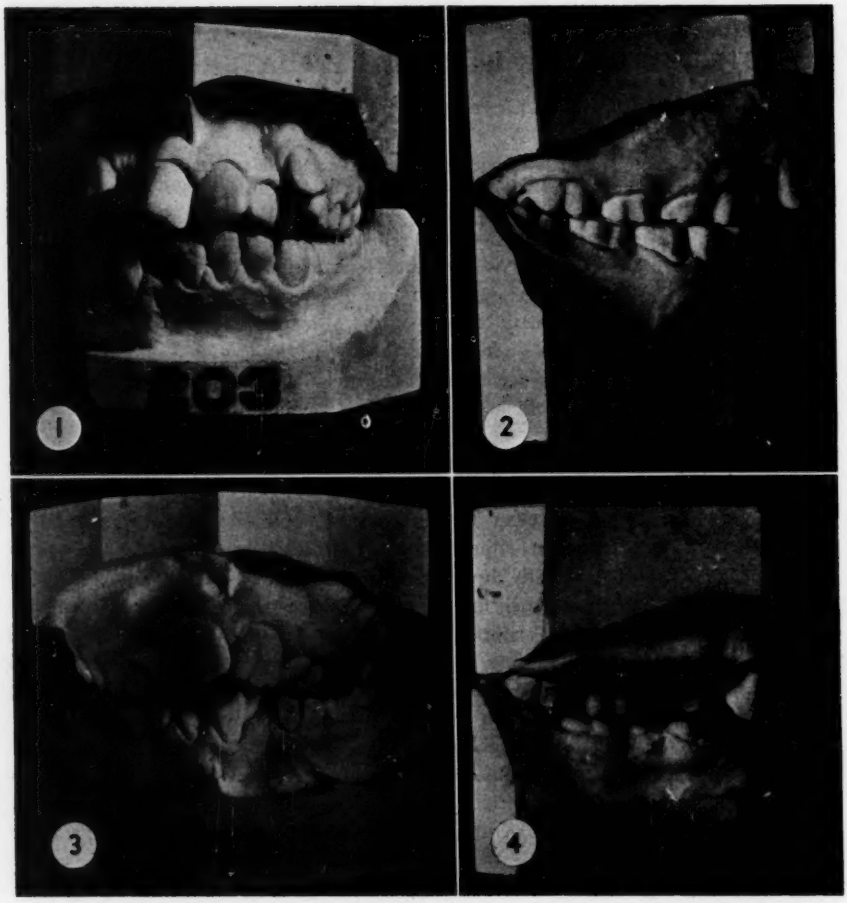


FIG. 1. Class I malocclusion (Angle). Development of upper and lower jaws is normal. Anteroposterior relationship of upper and lower teeth is correct, but individual teeth are malposed.

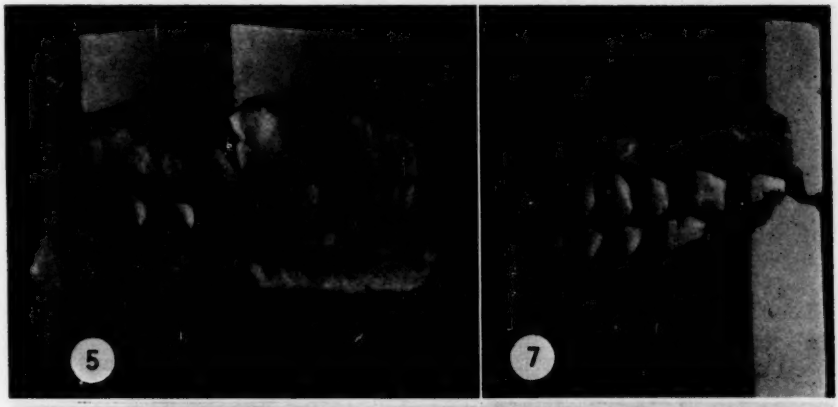
FIG. 2. Class II, Division I, malocclusion (Angle). Relationship of maxilla to mandible, as indicated by anteroposterior locking of upper and lower first molar teeth, is abnormal. Lower molar is half cusp or more posterior to normal, as it meets upper molar in occlusion. This is usually a developmental problem. Associated with improper jaw relationship is marked protrusion of upper incisor teeth and elongation of lower incisors, causing them to bite into soft tissue of palate. Hypotonicity of upper lip and hypertrophy of lower lip are additional deforming factors (see Fig. 6).

FIG. 3. Front view of plaster models in Fig. 2.

FIG. 4. Class II, Division II, malocclusion (Angle). Lower jaw position is half cusp or more posterior to normal in its relationship to upper jaw, as indicated by upper and lower first molar teeth. Frequently this is not a growth or developmental problem, but guiding of lower teeth and jaws into forced retrusion by excessive lingual inclination of maxillary incisor teeth. Associated with this type of dento-facial deformity is normal peri-oral musculature, square-shaped arches and teeth, and deep overbite resulting from deficient eruption of posterior teeth.

either the upper incisors protruding (Figs. 2 and 3) or retruding (Figs. 4 and 5). This group was usually characterized by an underdeveloped mandible, convex facial profile, hypotonic peri-oral musculature and poor function (Fig. 6). The third group, Class III, included all cases where the lower molars had assumed a position anterior to normal in their relationship to the upper molar teeth. These were the prognathous individuals, with upper front teeth biting within the lowers, with either maxillary retrusion, or mandibular protrusion (Fig. 7). Class II and Class III malocclusions usually involve jaw relationship primarily, so that a growth and developmental appraisal is quite important.

The pioneers in orthodontics recognized the importance of growth and attempted to arrive at some standard which could serve as a guide. The first efforts were anthropologic, using large samples of skeletal material. Hellman made the greatest contribution in his



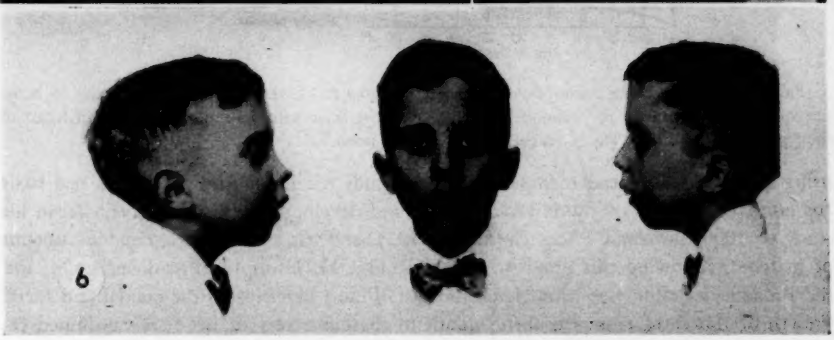


FIG. 5. Front view of Fig. 4. Lower teeth are completely hidden by deep overbite.

FIG. 6. Full face and profile views of patient with Class II, Division I, malocclusion. Note hypotonic, functionless upper lip and convex facial profile.

FIG. 7. Class III, malocclusion (Angle). Lower jaw position is half cusp or more anterior to normal in its relationship to upper jaw, as indicated by first molar teeth. In most instances, upper incisor teeth close behind lower incisors, instead of in front, when jaws are brought together. This malrelationship may be due to underdevelopment of maxilla, to excessive lingual position of upper front teeth, or to overgrowth of mandible. Class III malocclusion is usually reflected in facial profile, giving individual "bull-dog" prognathous type of chin.

exhaustive studies of Indian skulls.[2-11] He showed the differential growth rates that occur in the skull, with the calvarium being completed relatively early, leaving the face to emerge from beneath the cranium by virtue of a continued downward and forward vector supplied by the spheno-occipital synchondrosis and sutural proliferation. Cross sectional studies of dried skulls have their limitations, however. It was Todd who said, "A dead child is a defective child."[12] He challenged the use of skeletal material of unknown history in the infant and childhood range to determine the normal processes of growth. Scammon again demonstrated the differential growth rates of various parts of the body (Fig. 8).[13] Interestingly enough, it is noted that while the brain case follows the neural growth curve, the dento-facial component follows the general growth curve—with the exception of maxillary width, which is completed quite early. It remained for Broadbent,

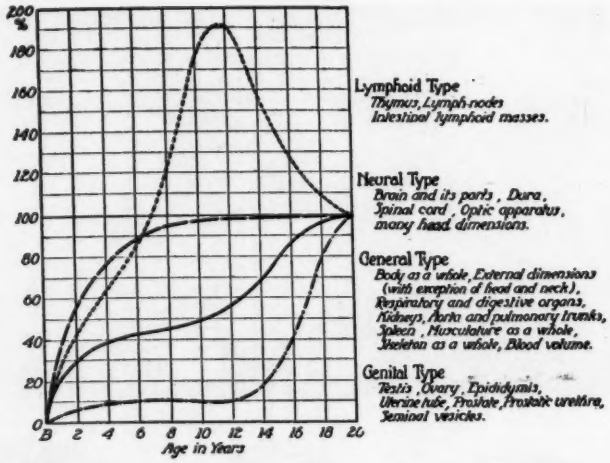


FIG. 8. Graph showing major types of postnatal growth of various parts and organs of body. Several curves are drawn to common scale by computing their values at successive ages in terms of their postnatal increments (to 20 years). (Courtesy, Scammon.[13])

using oriented serial head roentgenograms, to study the living and establish a real basis for normal standards of cranio-facial growth and development.[14-18] Broadbent began his study of 5000 Cleveland school children in 1931, and has amassed a tremendous amount of material, following this group to maturity (Fig. 9). Using the Broadbent series, and the Broadbent Bolton Cephalometer, Brodie at Illinois investigated the cranial and facial growth of the child from the third month to the eight year of life.[19-22] Continued research both at Illinois and Northwestern University on radiographic cephalometrics has increased our knowledge of normal and abnormal growth of specific areas of the dento-facial complex, both as to timing and increments.[23-35] Krogman has correlated both the anthropologic and radiographic cephalometric studies on facial growth patterns, showing the striking rhythm and fascinating complexity of the cranio-facial development.[36] Sicher,[37] Brash,[38] Schour[39] and others have helped to complete the picture with vital staining experiments and histologic studies of the actual sites of growth. We know now, for example, that the downward and forward growth of the maxilla is primarily due to the proliferation of sutural connective tissue, and its replacement by bone (Fig. 10).

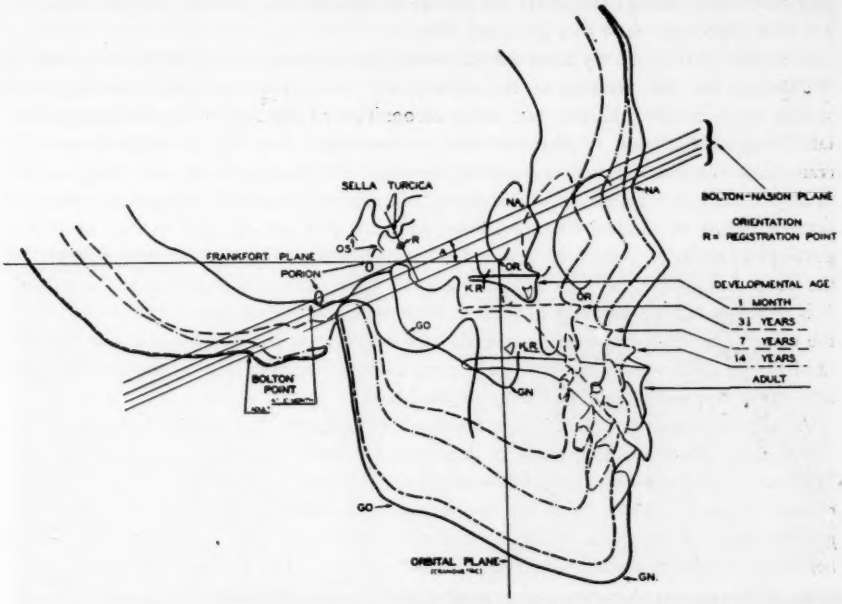


FIG. 9. Normal developmental growth of face from Bolton Study records of 3500 white Cleveland children. A. Angle of Frankfort plane of first tracing to Bolton-Nasion plane of orientation. Gn.-Gnathion. Go.-Gonion. K.R.-Key ridge. NA.-Nasion. OR.-Orbitale. OS.-Occipitosphenoidal suture.

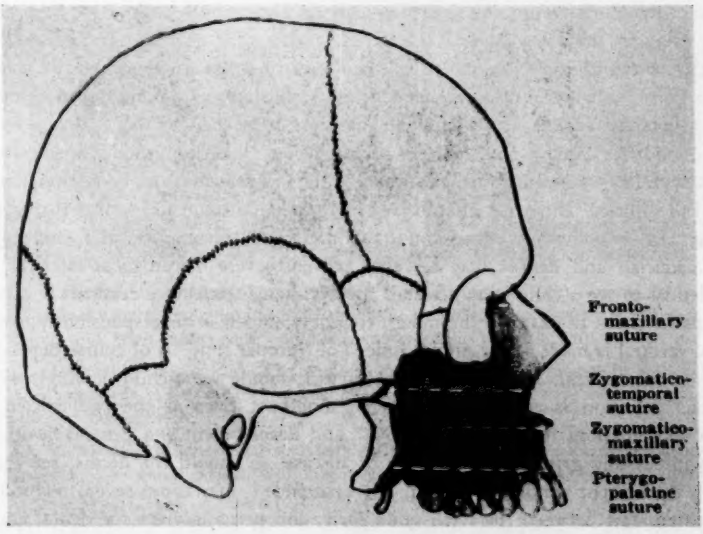


FIG. 10. Major sutural areas of maxillary development (Sicher). Proliferation of connective tissue in suture and its replacement by bone, propels maxilla downward and forward.

We understand rather completely the pattern of mandibular growth, and just what sites are most important—how they grow and when.

This all too brief survey of one of the most productive aspects of orthodontic research emphasizes that the problem of the orthodontist is so often not merely shifting teeth within their investing tissues, but rather recognition of the skeletal limitations, and establishing an occlusion of the teeth and a masticatory function in harmony with the cranio-facial morphology. It is possible to predict the facial pattern quite early in life. While studies of treated and nontreated orthodontic problems demonstrate that the present means of mechanotherapy cannot stimulate jaw growth, per se, that an underdeveloped mandible cannot be restored to normal size, these same studies demonstrate the successful guiding of the remaining growth increments in the maxilla and mandible. It is thus possible to withhold or redirect growth of one jaw to make it better conform to the other. The degree of success depends on the timing of the therapy. It is also possible to shift the teeth within the jaws to a more favorable relationship to one another. The aims of therapy will be discussed in more detail later.

As with so many departures from the normal constantly confronting the pediatrician, considerable effort has been made to determine the causes of dento-facial abnormalities. The frontiers of our knowledge on etiology are still not very far away. There are some obvious factors, however, that can be definitely established. Cephalometric roentgenographic studies have shown a striking pattern similarity in offsprings. There is a strong hereditary tendency for certain types of malocclusion. This is especially true of those cases primarily due to abnormal jaw relationships, the underdeveloped mandible, the prognathous lower jaw. It is often said that a child has inherited the teeth from the father and the jaws from the mother. As unscientific as this sounds at first, growth studies seem to substantiate this premise to some extent. It does seem possible to inherit certain facial characters from one parent, different characters from the other parent, and produce a dysplastic compromise. Experiments on Drosophila, or fruit fly, have produced bizarre changes with crossing of the genes, and guided pairing. The infinitely more complex mechanism of inheritance in man mitigates against extremes in genetic recombination, but there are strong tendencies established, and it is not unreasonable to look to heredity as the major etiologic basis of some dento-facial deformities. More positive evidence can be produced for malocclusions resulting from congenital diseases such as syphilis, from nutritional disturbances such as rickets, from endocrinopathies and from birth injuries. There are a number of local and environmental factors that are within the realm of orthodontics. More important, their early recognition and interception by the pediatrician and dentist may serve to prevent severe disturbances later. It is wise for a dentist to see a child soon after all the deciduous teeth have erupted. It is the duty of the pediatrician to examine the mouth routinely, and it is his responsibility to see that a dental referral is made at the proper time. The "proper time" is of course dependent on the reason for referral. A dentist, or orthodontist, should see a child definitely when the deciduous dentition is complete (24 to 30 months). Even as the pediatrician makes periodic examinations to observe the growth and development and general health of the child, without any *prima facie* evidence of disease, so should the dentist see the child routinely to prevent conditions which, left unattended, may cause severe malocclusions. Caries often start between the teeth quite early, and periodic visits for dental check-ups after 2½ years of age will serve a twofold purpose: prevent premature loss of deciduous teeth through caries, with resultant malocclusion, and secondly to foster the development

of a friendly relationship built on confidence, not fear. This is especially true if nothing has to be done at first—it is quite important.

The premature loss of deciduous teeth is one of the major etiologic factors in dental malocclusions. The delicate and complex timetable of tooth formation, tooth eruption, root resorption and tooth loss, all taking place in a rapidly growing medium, can be upset easily. The early loss of deciduous teeth before they are to be shed normally almost always results in the loss of space, preventing the succedaneous tooth or teeth from assuming normal position, or from erupting at all. The drifting of the remaining teeth,

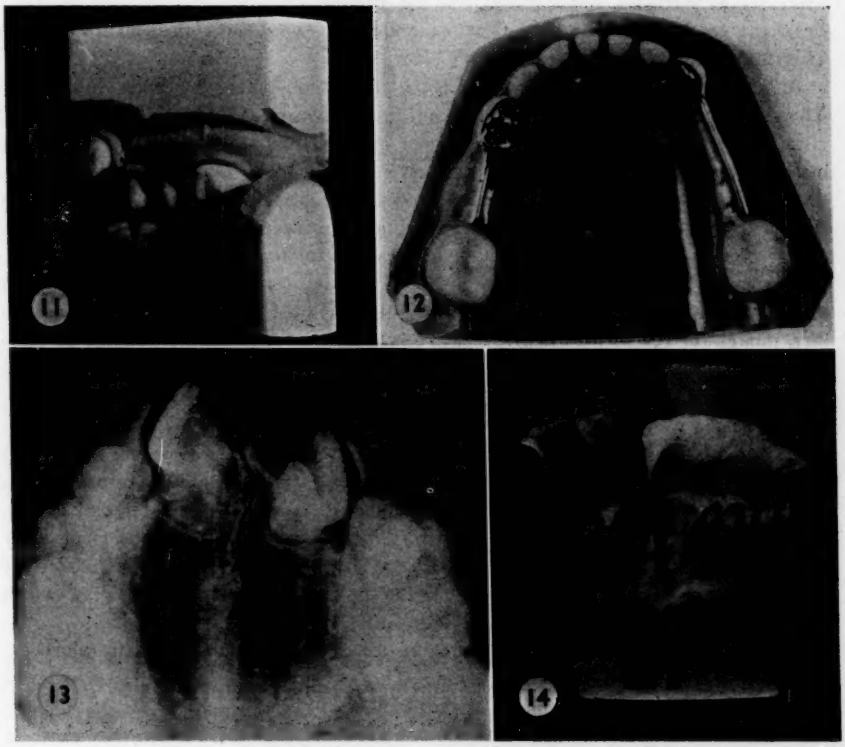


FIG. 11. Early loss of deciduous cuspid allowed posterior teeth to drift forward into space left. Permanent cuspid was left with insufficient room in arch and erupted completely out of arch, high in muco-buccal fold. Space maintenance would have prevented this malocclusion.

FIG. 12. Model of space maintaining appliance, holding space left by premature loss of deciduous molars, until bicuspids erupt. First permanent molars would drift forward into this space, if left alone, impacting bicuspid teeth.

FIG. 13. Radiograph of unerupted maxillary central incisors. Note supernumerary tooth lying diagonally across one central incisor, with fragments of supernumerary tooth lying in palate behind other incisor.

FIG. 14. Malocclusion resulting from prolonged retention of deciduous teeth. Medical history showed hypothyroid tendency and delayed eruption pattern. Both deciduous upper right central incisor and lower left lateral incisor had to be extracted.

because of the premature loss of one or more dental units, can be enough to interfere with the development of the entire dental arch. The developing malocclusion fosters inadequate or improper habits of mastication and almost always increases caries susceptibility and gingival disturbances (Fig. 11). Soon after the first visit, the dentist should take complete intra-oral radiographs, and continue to take them at yearly intervals. By so doing, he can check on a number of possible causes of dental malocclusion. Congenital absence of teeth (especially upper lateral incisors and bicuspid teeth) is relatively common. Generally, a hereditary tendency is noted. Radiographs can quickly reveal this absence during the developmental stages, and steps can be taken to maintain the deciduous tooth, or the space for its successor. Space maintainers are also used where it is impossible to save a deciduous tooth from early loss, to maintain the space until the permanent tooth erupts (Fig. 12).

Another cause of malposition of teeth is the presence of supernumerary teeth (Fig. 13). They can range from perfect "extra" teeth to cystic masses, but their presence almost always upsets the eruption of the contiguous teeth. Here, too, radiographic recognition means early surgical interception, and prevention of the malocclusion. Occasionally, deciduous teeth are retained past the time they should normally be shed. This is especially true in hypothyroid children. Prolonged retention can mean the eruption of the permanent successor into the palate, or into the muco-buccal fold (Fig. 14). Prolonged retention may be due to the formation of a bony bridge between tooth and the alveolar process, causing an ankylosis. In these cases, the ankylosed tooth doesn't erupt any further, though the rest of the teeth normally continue to erupt constantly with the development of the alveolar process. The result is a "submerging tooth," finally covered by the mucosa, as if it had never been in the mouth. These teeth can badly disrupt an occlusion, and are missed all too often by pediatricians and dentists.

Sometimes the deciduous teeth are shed on schedule, but the permanent teeth don't follow into place. Delayed eruption of permanent teeth may be due to the formation of a bony barrier over the occlusal surface of the tooth, or simply a fibrous mucosal barrier. As with retained deciduous teeth, hypothyroid individuals also show a strong tendency toward delayed eruption of permanent teeth. The pediatrician might well take this latter condition as a strong clinical sign of an endocrine disturbance, at least worth checking.

Most pediatricians have been confronted at one time or another by parents who were concerned about thumb and finger sucking. That it is considered a confusing problem is seen in the following paragraph by Langford:

"Thumb and finger sucking are of importance because of the concern they cause in parents. The pediatrician to whom the alarmed parents come for advice is often as confused about the significance of the practice as are the parents themselves. He finds it difficult to help them or allay their fears. In order to do this successfully, he is in need of a working knowledge of the significance of the habit at different age levels. He needs to know what harm, if any, may result; what factors lead to the development of the habit, and what measures should, or should not be taken to handle the situation adequately."[40]

Much of the controversy is due to the lack of liaison between medicine, dentistry, and psychiatrics. Claims and counter claims have no common basis of appraisal. This subject has been elaborated on by the author in a recent article,[41] and can be summarized in a few sentences. Thumb and finger sucking can be considered as an expression of the in-

fant's hand-to-mouth movement, normal in most instances for the first 12 to 18 months, and as far along as the third year in some individuals. Some youngsters learn to rely on these habits for release of emotional tension beyond this time, to the detriment of the health and configuration of the teeth and jaws. These habits are frequently made more pronounced by constant parental badgering and half-hearted unguided attempts to stop the sucking, converting the habit into an attention-getting mechanism for the child. It is felt that no parent should admonish the child to stop the habit, especially before the

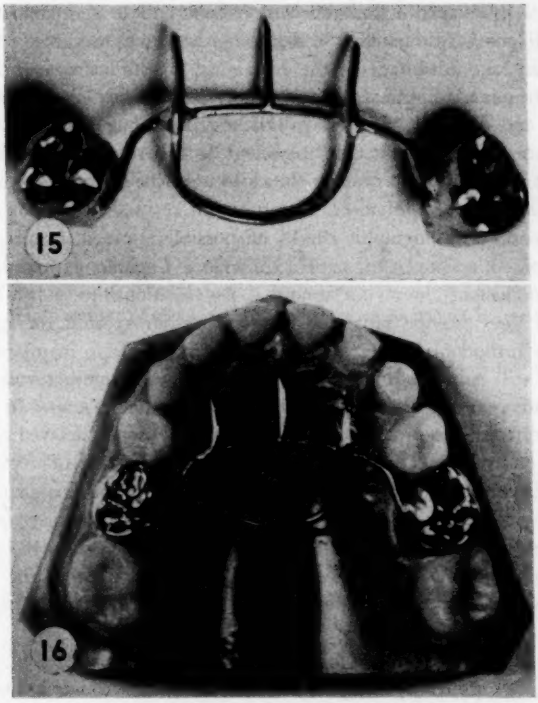


FIG. 15. Anti-thumb and finger-sucking device, placed on maxillary deciduous molar teeth to prevent deformation of premaxillary segment and to break habit pattern.

FIG. 16. Thumb-sucking device mounted on model. Projecting spurs are bent toward palate and are turned downward only if habit persists.

third year of life, for the danger of increasing the persistence and duration of the habit is greater. The damage done by the habit depends on the duration, intensity and persistencse of the thumb and finger sucking. If a developing malocclusion is already present, the abnormal pressures of the habit will serve to increase the degree of deformity. This damage can be quite severe. In almost all cases, the abnormality results when the sucking habit is continued beyond the third year. If the child is left completely alone, with complete parental indifference, the thumb and finger sucking usually disappear spontaneously by the end of the third year of life, and any damage to the teeth and arches that occurs usually is corrected in the permanent dentition. The frequent claims of habit transference, psychic trauma and adult neuroses as a result of attempts to break the habit cannot

be substantiated by studies at Northwestern University. Therapy, however, has to be direct, properly guided, with full parental indoctrination as to the proper course to follow at home. The use of a simple mechanical device, placed across the roof of the mouth, has been uniformly successful (Figs. 15 and 16).

The problem of therapy for malocclusions has already been mentioned in connection with growth and development of the cranio-facial area. With the limited means at his disposal, the orthodontist must take advantage of every physiologic phenomenon in his favor, if he is to be successful. In malocclusions where there is an abnormal jaw relationship, an early diagnosis is imperative so that the orthodontist may intercept the developing abnormality, and take advantage of the remaining growth increments by guiding them by means of orthodontic appliances. In severe dysplasias, therapy is indicated as early as three years of age. Fortunately, there is little discomfort and no pain attached to corrective procedures, so that patient management at this time presents no problem. Frequently, it may be necessary to observe the child until the teeth have erupted far enough to allow the placement of appliances. This time can be used to develop correct habits of oral hygiene, to make radiographic checks on possible etiologic factors, to see that oral health is maintained, and to instill patient confidence. Cephalometric radiographic studies of treated malocclusions, involving abnormal jaw relationships, in children between 3 and 8 years of age, provide satisfying evidence of our greatest therapeutic assistance. There are many orthodontic problems where it is impossible to maintain all the teeth in the mouth and still gain a normal balanced occlusion. The mother will bring her child to the orthodontist, saying, "Johnnie's teeth are too big for his jaws." In lay terminology, this may be a correct diagnosis. In such cases, therapy is usually delayed until the eruption of the 12 year molars. Even in these problems, serial extraction of deciduous teeth may be resorted to between 7 and 12 years of age to lessen the ultimate time of treatment. Most orthodontic cases take between 12 and 30 months for full correction. To move the teeth too fast endangers both the teeth and the surrounding tissues. If handled properly, dental caries susceptibility is actually lessened during treatment by the covering of the susceptible interproximal areas by the appliances, and by more rigid oral hygiene. The latter is a "must," however.

Now, what are the eventualities, providing orthodontic treatment is not undertaken? Ample evidence is supplied by the periodontist—the dentist concerned with the gingival disturbances and loss of supporting bone around the teeth. Teeth in abnormal position are more susceptible to dental caries. Teeth in abnormal position are subject to abnormal stresses and traumatic masticatory forces, and ultimately break down from the undue stress. Or, there may be impaired or inadequate function due to a dental malocclusion, with premature atrophy of the alveolar process as an ultimate consideration. By the time the patient reaches the periodontist, it is usually too late to restore the teeth to their normal position and inclination, so that therapy only temporizes, prolonging the inevitable time for an artificial replacement.

In summary, orthodontics plays an important role in maintaining and restoring oral health and function by placing the teeth in their proper positions. In most cases, dental malocclusions are actually due to malrelationships of the jaws themselves, and require corrective procedures which guide growth increments of the maxilla and mandible. An important phase of orthodontics is prophylactic—recognizing the developing etiologic factors and intercepting them before the disturbance becomes severe. The pediatrician and dentist have a responsibility in maintaining normal development of the stomatog-

nathic system. Specifically, the dentist should see the child after completion of the deciduous dentition, and continue to observe him not less than once a year. Orthodontic consultation is required:

(1) When there is any congenital disturbance or birth injury that can produce facial deformity (e.g., cleft palate, hydrocephalus).

(2) When severe nutritional disturbances are present (e.g., avitaminoses).

(3) When endocrinopathies are diagnosed (e.g., hypothyroidism).

(4) When there has been premature loss or prolonged retention of the deciduous teeth—or any developmental abnormality (e.g., growth disturbances, supernumerary teeth, congenital absence, frenum diastemas).

(5) When abnormal environmental or behavior habits are producing a dento-facial deformity (e.g., thumb and finger sucking, mouth breathing).

Orthodontic therapy has severe limitations, and must be instituted at the proper time to gain the best possible results. This may be anywhere between 3 and 12 years, depending on the nature of the problem.

References

1. Angle, E. H., Malocclusion of Teeth, ed. 7, Philadelphia, S. S. White Company, 1907.
2. Hellman, M., Interpretation of Angle's classification of malocclusion of teeth, Dental Cosmos **62**:476, 1920.
3. Hellman, M., Orthodontia, its origin, evolution and culmination as specialty, Dental Cosmos **62**:14, 1920.
4. Hellman, M., Changes in human face brought about by development, Internat. J. Orth. & Oral Surg. **13**:475, 1927.
5. Hellman, M., Face and teeth of man, J. Dent. Research **9**:179, 1929.
6. Hellman, M., Introduction to growth of human face from infancy to adulthood, Internat. J. Orth. & Oral Surg. **18**:777, 1932.
7. Hellman, M., Face in its developmental career, Dental Cosmos **77**:685, and 777, 1935.
8. Hellman, M., Growth of face and occlusion of teeth, Internat. J. Orth. & Oral Surg. **19**:1117, 1933.
9. Hellman, M., Some biologic aspects, Internat. J. Orth. & Oral Surg. **23**:785, 1937.
10. Hellman, M., Some facial features and their orthodontic implications, Am. J. Orth. & Oral Surg. **25**:927, 1939.
11. Hellman, M., Development of Occlusion, Philadelphia, W. B. Saunders Company, 1941.
12. Todd, T. W., Orthodontic value of research and observations in developmental growth of face, Angle Orthodontist **1**:67, 1931.
13. Scammon, R. E., and others, Measurement of Man, Minneapolis, University of Minnesota Press, 1930.
14. Broadbent, B. H., New technique and its application to orthodontia, Angle Orthodontist **1**:45, 1931.
15. Broadbent, B. H., in Dewey, M., Practical Orthodontia, revised by G. M. Anderson and others, ed. 5, St. Louis, C. V. Mosby Company, 1935.
16. Broadbent, B. H., Face of normal child, Angle Orthodontist **7**:185, 1937.
17. Broadbent, B. H., Bolton standards and technique in orthodontic practice, Angle Orthodontist **7**:212, 1937.
18. Gregory, W. K., Broadbent, B. H., and Hellman, M., Development of Occlusion, Philadelphia, W. B. Saunders Company, 1941.
19. Brodie, A. G., Some recent observations on growth of mandible, Angle Orthodontist **10**:63, 1940.
20. Brodie, A. G., On growth patterns of human head, Am. J. Anat. **68**:209, 1941.
21. Brodie, A. G., On growth of jaws and eruption of teeth, Angle Orthodontist **12**:109, 1942.
22. Brodie, A. G., and Ortiz, M. H., On growth of human head from birth to third month of life, Anat. Rec. **103**:311, 1949.
23. Brodie, A. G., Growth patterns of human head from third month to eighth year of life, Thesis, Chicago, University of Illinois, 1940.

24. Baldridge, J. P., Study of relationship of maxillary first permanent molar to face in class I and class II malocclusions, Angle Orthodontist **11**:105, 1941.
25. Bushra, E., Variations in human facial pattern in normal lateralis, Thesis, Chicago, University of Illinois, 1947.
26. Noyes, H. J., Rushing, C. H., and Sims, H. A., Axial inclination of human central incisor teeth, Angle Orthodontist **13**:60, 1943.
27. Blume, D. G., Roentgenographic study of position of mandible in malocclusion of teeth, Thesis, Chicago, Northwestern University, 1947.
28. Boman, V. R., Roentgenographic study of position of mandible in normal occlusion of teeth, Thesis, Chicago, Northwestern University, 1948.
29. Thompson, J. R., and Brodie, A. G., Factors in position of mandible, J. Am. Dent. A. **29**:925, 1942.
30. Thompson, J. R., Rest position of mandible and its significance to dental science, J. Am. Dent. A. **33**:180, 1946.
31. Thompson, J. R., Oral and environmental factors as etiologic factors in malocclusion of teeth, Am. J. Orth. **35**:33, 1949.
32. Mayne, W. R., Study of skeletal pattern of human face, Thesis, Chicago, Northwestern University, 1946.
33. Downs, W. B., Variations in facial relations and their significance in treatment and prognosis, Am. J. Orth. **34**:10, 1948.
34. Riedel, R. A., Cephalometric analysis of anthropometric and craniometric measure points, Thesis, Chicago, Northwestern University, 1948.
35. Freeman, R. G., Radiographic method of analysis of relation of structures of lower face to each other, Thesis, Chicago, Northwestern University, 1951.
36. Krogman, W. M., Facing facts about face growth, Am. J. Orth. & Oral Surg. **25**:724, 1939.
37. Sicher, H., and Weinmann, J., Bone and Bones, St. Louis, C. V. Mosby Company, 1947.
38. Brash, J. C., Growth of jaws in health and disease, London, Dental Board of United Kingdom, 1924.
39. Schour, I. M., Post-natal cranio-facial and skeletal development as demonstrated by vital injections of alizerine red S, Anat. Rec. **76**:94, 1940.
40. Langford, W. S., Problem of thumb and finger sucking, Am. J. Dis. Child. **58**:1290, 1939.
41. Graber, T. M., Logical approach to problem of thumb and finger sucking, to be published.

SPANISH ABSTRACT

Problemas de Ortodoncia en la Práctica Pediátrica

Una de las manifestaciones mas importantes del estado de salud de la boca es su forma y su normalidad funcional mecánica. Frecuentemente las posiciones defectuosas de los dientes o las maloclusiones bucales no hacen sino reflejar un trastorno del crecimiento y desarrollo del maxilar y la mandíbula. Los dientes defectuosos son invisibles, pero lo que es mas importante, probablemente funcionan en forma inadecuada o no tienen función alguna lo cual interfiere seriamente con la salud y longevidad de los otros dientes y sus tejidos de envoltura. Estudios recientes del crecimiento facial indican que las oclusiones dentales defectuosas pueden ser agrupadas en tres grupos morfológicos en función del desarrollo de los maxilares y de las malposiciones individuales dentales. Primero, las maloclusiones cuya naturaleza es primariamente genética, en las cuales existe una relación anormal entre uno y otro maxilar, generalmente a consecuencia de una disarmonía cronológica de su desarrollo normal. Los dientes de cada arco dental pueden estar en posición normal cuando se les compara con su maxilar de implantación pero la articulación de ambos maxilares es anormal lo cual determina que los superiores no afronten con los inferiores en forma adecuada durante la masticación, deglución y lenguaje. El segundo grupo lo forman alteraciones relativamente locales en las que los dientes están colocados incorrectamente pero la articulación de los maxilares es normal. El tercer groupo es una combinación de los dos primeros pues simultáneamente existe una relación mandibular inadecuada y dientes en posición anormal. Dentro de estas tres grandes categorias se pueden encontrar toda clase de anomalías de posición de los dientes y de la articulación interdentomaxilar; el segmento premaxilar puede estar desplazado anteriormente, el arco inferior en retrusión, los incisivos superiores hacer erupción en el paladar, etc., anomalías que pueden presentarse por separado u ocurrir en combinación.

Los estudios antropológicos de los índices de crecimiento de varias partes del cuerpo, y aquellos

que han establecido los standars normales del crecimiento y desarrollo craneo facial, etc. etc. permiten entender en la actualidad, en forma mas o menos completa, cual es el patrón del crecimiento mandibular y precisamente que sitios son los mas importantes, como y cuando crecen, enfatizando que el verdadero problema del ortodoncista no es frecuentemente el de desplazar dientes con sus tejidos de envoltura sino más bien el de reconocer las limitaciones del esqueleto y establecer una oclusión de los dientes y una función masticatoria en armonia con la morfologia craneo facial. Es posible en la actualidad predecir el patrón facial bastante temprano en la vida y aunque los estudios de los problemas ortodónsicos no tratados demuestran que los medios actuales de mecanoterapia no pueden estimular el crecimiento incompleto de los maxilares, es decir, restaurarles su tamaño normal, los mismos estudios demuestran con cuanto éxito se pueden guiar los incrementos de crecimiento que aun faltan por realizarse. Así pues, es posible detener o dirigir correctamente el crecimiento de uno de los maxilares para que articule mejor con el otro dependiendo el grado de éxito que se alcance de la oportunidad de la terapeútica. También es posible desplazar los dientes de un mismo maxilar en una posición mas favorable con respecto de uno al otro.

En cuanto a la etiología de estas anormalidades dentofaciales se han encontrado varios factores que pueden considerarse definitivamente. Primero, la tendencia hereditaria marcada en ciertos tipos de maloclusión respaldada por experimentos en herencia. Segundo, padecimientos congénitos que pueden producir maloclusiones como la sífilis, de trastornos nutricionales como el raquitismo, de endocrinopatías y de traumatismos al nacimiento. Tercero, el desarrollo de caries que con frecuencia se inicia bastante temprano, que produce la caída prematura de los dientes deciduales permitiendo la pérdida del espacio de los dientes definitivos, interfiriendo con el desarrollo normal del arco dental favoreciendo hábitos inadecuados de masticación, aumento de la susceptibilidad a las caries y trastornos gingivales. La presencia de piezas supernumerarias es otro de los factores que producen posiciones inadecuadas de los dientes. En ocasiones la persistencia de los dientes deciduales o la ausencia de erupción de los permanentes como puede suceder en niños hipotiroideos, produce un diente permanente sumergido que deforma una oclusión que fué correcta.

Otra causa de oclusión defectuosa de la boca y aun de los dientes es el hábito muy frecuente de la succión de los dedos. Existe cierta desorientación en cuanto a la importancia de este hábito y las deformaciones que causa. Estas dependen de la duración, persistencia e intensidad de dicha costumbre, mas aún, si ya existe una maloclusión en desarrollo dicho hábito la agravará al grado de hacerla bastante severa. Al pediatra corresponde hacer la prevención del mismo sabiendo, en primer lugar, que es un acto normal en la mayor parte de los niños durante los primeros 12 ó 18 meses y aun hasta el tercer año en algunos casos; segundo, que su persistencia después de los 3 años es lo que realmente produce las anormalidades citadas y por último, que una de las causas fundamentales que determinan que el hábito se perpetúe es cuando el niño tiene un estado de tensión emocional y lo usa como un mecanismo de canalización o, lo que es mas importante aun, cuando es realizado por el niño para llamar la atención del medio familiar como una reacción a la presión que los padres ejercen para detenerlo. El papel del pediatra es el de instruir y calmar los temores de los padres para que no traten de impedir dicha costumbre ni antes y menos después de los tres años de edad y que lo dejen en libertad, pues en la mayor parte de los casos lo olvidará espontáneamente.

En conclusión, la ortodoncia desempeña un papel muy importante manteniendo o restaurando la salud bucal y su función, colocando los dientes en posición apropiada, usando de procedimientos correctivos para guiar los incrementos del crecimiento de los maxilares, previniendo las maloclusiones dentales, reconociendo y tratando los factores etiológicos que las producen. Específicamente, el dentista debe ver al niño después de terminada la dentición decidual y continuar su observación cuando menos una vez al año. La consulta ortodóncica debe buscare 1).—Cuando exista un trastorno congénito o traumatismo obstétrico que puedan producir una deformidad facial (v.g. paladar hendido, hidrocefalia). 2).—Cuando se presenten trastornos nutricionales severos (v.g. avitaminosis). 3).—Cuando se ha hecho el diagnóstico de endocrinopatías (v.g. hipotiroidismo). 4).—Cuando haya pérdida prematura o retención prolongada de los dientes deciduales o cualquier anormalidad en el desarrollo. (v.g. trastornos del crecimiento, dientes supernumerarios, ausencia congénita, etc.) 5).—Cuando un ambiente anormal o trastornos de conducta del niño esten produciendo una deformidad dentofacial (v.g. succión de los dedos, respiración bucal).

Como la terapeútica ortodóncica padece de severas limitaciones debe ser instituida con oportunidad para obtener los mejores resultados y ésto puede ser en cualquier momento entre los 3 y 12 años, dependiendo de la naturaleza del problema.

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AGAMMAGLOBULINEMIA

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THE complete absence of gamma globulin in human serum with a normal total protein as determined by electrophoretic analysis does not appear to have as yet been reported in the literature. Stern[1] mentions two cases of hypoproteinemia in children who had "almost complete absence of gamma globulin and were singularly free from infection." Schick[2] reported a similar congenital case without nephrosis with a review of the literature in which the total protein was low, the gamma globulin fraction low, and edema present. The latter findings in nephrosis are well known. Krebs[3] reported a case in which there was a "depression or gamma globulin in hypoproteinemia due to malnutrition." The present author had the opportunity of following a patient without nephrotic syndrome, with normal nutrition, with complete absence of the gamma globulin fraction and normal total serum protein through several years of many infections, including 19 episodes of clinical sepsis in which some type pneumococcus was recovered by blood culture 10 times. This entity, which, it was found, could be controlled by supplying gamma globulin as contained in concentrated immune human serum globulin, appears to be unique.

CASE REPORT

This 8 yr. old male was first admitted to this hospital at the age of 4½ yr. His past history was rather normal. He had varicella 8 mo. before admission with uneventful recovery and rubeola complicated by pneumonia 6 mo. previously. His birth and developmental history were entirely normal and a general survey of the major systems revealed nothing of note. The family history revealed no deviation from normal and a 1 yr. old sibling was in good health. He was considered a normal and healthy child until 2 nights before admission when he came in from play and had a short shaking chill followed by a rise in temperature to 38.1°C. The next day he vomited, his fever continued and he complained of pain in the left knee. A physician was consulted and prescribed aspirin, stating that the child might have rheumatic fever. There was no improvement and his fever rose to 38.8°C. after 24 hr. and admission was advised. On admission and physical examination he appeared well-developed, well-nourished and moderately ill. His face was flushed. His temperature was 38.3°C., pulse 110/min., respirations 22/min. and blood pressure 100/60 mm. Hg. There were 10 to 15 tiny petechiae on the flexor surfaces of both arms prior to application of blood pressure cuff, but the parents were not aware of any trauma or tourniquet having been applied. There was no glandular enlargement and eye, ear, nose and throat examinations were normal except for mild hyperemia of nasal and pharyngeal mucous membranes. The chest, heart and abdomen were normal. The extremities were normal with the exception of the left leg which showed no redness, swelling or increased heat, but the patient complained of intense pain on attempted motion of the knee joint.

His hemogram showed RBC count 4.2 million/cmm., Hgb. 12.4 gm./100 cc., WBC count 16.4 thousand/cmm., with 88% neutrophiles (5 stabs), 8% lymphocytes and 4% monocytes. Urine was normal. Blood culture was negative after 10 days' incubation. RGs of both lower extremities including hips were normal. ECG was normal.

The impression was that he had either a septic joint or osteomyelitis. After the initial studies, he was given penicillin, 300,000 units twice daily, for 28 days. He continued to have fever up to 38.8°C. for 2 days after starting therapy. The symptoms in the left leg disappeared concurrently and he seemed well. Although serial RGs continued to show no bony defect, it was felt osteomyelitis was the most likely diagnosis at the time of discharge.

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He remained well at home for approximately 2 wk. at which time he developed an upper respiratory infection which is said to have developed into pneumonia. His temperature rose to 40.0°C. and he was treated with sulfa drugs for 5 days and had one dose of penicillin. On the fourth day of this illness he developed a swelling of the left jaw which his family doctor diagnosed as epidemic parotitis. Upon recovery from this episode he remained well for 10 days and then developed a violent gastrointestinal upset with a temperature rise to 40.5°C. and severe vomiting.

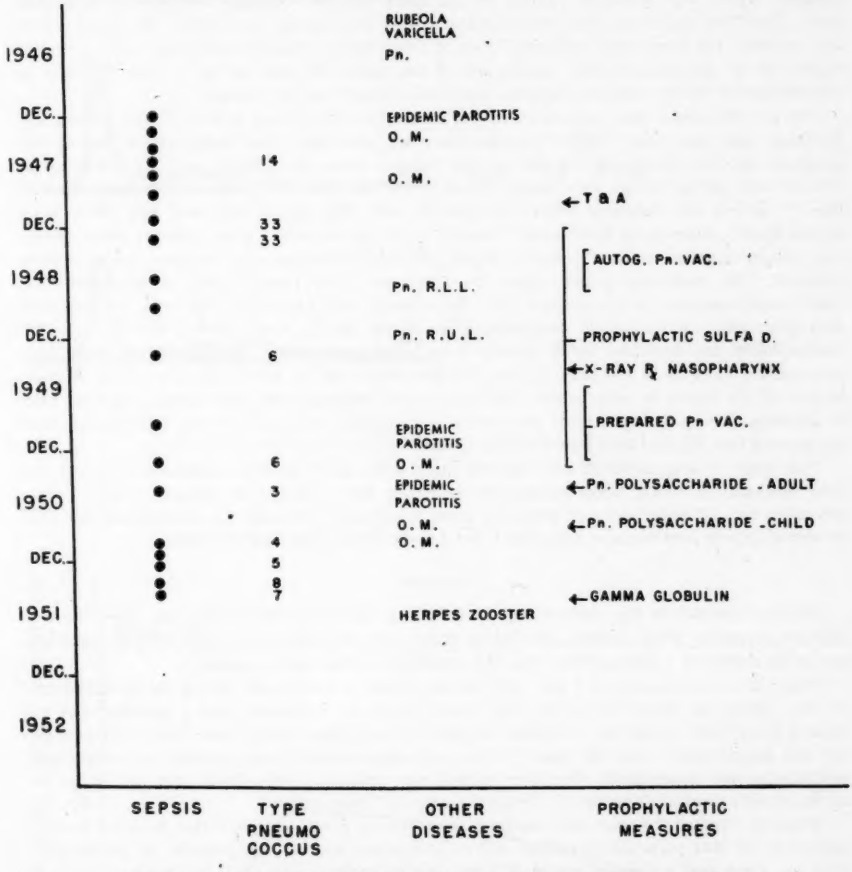

CHART 1. To show date of clinical sepsis, type pneumococcus recovered from blood culture, and prophylactic measures used.

He was again treated at home with sulfonamides and responded well in 4 to 5 days. He remained well only a week or so when a similar episode of fever and vomiting occurred. He continued to run a febrile course with daily rises in temperature to 38.8°C. for 2 wk. when he began complaining of earache. Again sulfonamides were administered by his family physician with apparent recovery. Sulfadiazine was continued 1 gm. daily for 2 wk. and he remained well. However, upon stopping medication for 36 hr. he again developed fever and was admitted a second time to the hospital.

The essential findings on this second admission were decreased light reflex in tympanic membranes bilaterally, with the left one bulging. The latter was incised. Given penicillin in oil and beeswax, 300,000 units daily, he responded rapidly. A blood culture on admission was positive for

type XIV pneumococci. A throat culture yielded the same type pneumococcus as did pus from the incised drum. A blood culture on the fourth day of treatment was negative. He was treated for 10 days and discharged in apparently good condition.

Two months later he developed otitis media again and was treated with sulfadiazine on an outpatient basis. Two days after discontinuing the drug, he was admitted to the hospital with a temperature of 40.0°C. and pain in the left shoulder. The only positive finding was confined to his shoulder which was extremely painful on attempted motion, requiring morphine to keep him quiet. The WBC count was 25.0 thousand/cmm., 91% neutrophiles (16 stabs). The blood culture was negative. His temperature rose rapidly to 41.6°C. shortly after admission, but dropped sharply within 48 hr. on penicillin and sulfadiazine. It was again felt that he had a septic shoulder or osteomyelitis of the left humerus; however, serial RGs revealed no bony changes.

The next admission was precipitated by the usual onset of fever up to 41.0°C. and without any localizing signs and type XXXIII pneumococcus was recovered from blood culture. During this admission he was thoroughly studied for any possible focus of infection or other pathology by systematically going through each system. These studies included ear, nose, and throat surveys with RGs of sinuses and mastoids, dental examination with RGs, spinal tap, skull RG, EEG, ECG, bronchograms, intravenous pyelograms, repeated urine examinations, urine cultures, stool culture and examination for ova and parasites, blood chemistry including urea nitrogen, serum protein, chlorides, CO_2 combining power, sugar, bromsulphalein liver function test, sedimentation rate, febrile agglutinations, antistreptolysin titer, Brucellergin and tuberculin skin tests, malaria thick drop preparation, and complete roentgenographic skeletal survey. Consultations with various services including ear, nose and throat, dental, chest, heart, genitourinary, orthopedic, and neurologic, produced no clues as to the cause of his difficulty. Although his tonsils did not appear diseased, because of his history of otitis media, tonsillectomy and adenoidectomy was advised and done prior to discharge. The pathologic report was normal for adenoid and tonsillar tissue. Subsequently bone marrow and liver biopsies have shown normal tissues.

This story of hospitalization was repeated many times and a plan of outpatient treatment was later developed in which, upon presentation with chill, fever and general malaise, a blood culture was taken and 1,000,000 units of penicillin given intravenously through the same needle, followed by several days of intramuscular penicillin. Chart 1 shows briefly these many episodes.

Method

The first approach to this problem was by a thorough search for foci of infection. However, with different organisms being isolated, one had to hypothecate the existence of a mutation of organisms, and in the absence of a demonstrable focus this possibility seemed highly untenable.

Prophylactic sulfadiazine, in 1 gm. daily dosage, failed to control and during the period covered by this attempt at control the patient had clinical sepsis on 6 occasions and a pneumococcus was isolated from blood culture on 3 of these occasions. There appear to have been fewer infections during this period, but it was felt that his basic difficulty was not being attacked and prophylactic sulfadiazine was discontinued. Penicillin aerosol was attempted periodically, but had to be discontinued after short trials because of the development of "hairy tongue."

When he repeated the same type organism in an illness, it was suggested that he failed to build antibodies for that particular organism and an autogenous vaccine was prepared of pneumococci. This was given over a planned period of 5 mo., but no antibody titer could be demonstrated in his blood serum at the end of this period. When more types of pneumococci were discovered as causing sepsis, a vaccine was prepared containing 6 types of pneumococci and was given over a period of 7 mo. However, again antibody titers for the specific organisms could not be demonstrated. It seemed possible that such a prepared vaccine would not contain sufficient immunizing antigen, i.e., the polysaccharides. Consequently the pneumococcal polysaccharide solution of Squibb, containing types I, II, III, V, VII and VIII in one for adults and types I, IV, VI, XIV, XVII and XIX in the other for children, were given at spaced intervals. Again no pneumococcus type antibody could be demonstrated in the patient's serum.

The question naturally arose then as to whether he could build antibodies against any organism. A Schick test was positive at 8 yr. of age although the patient had had a diphtheria toxoid series administered in infancy and had booster doses at 3 yr. of age and again at 6. A third and fourth booster dose failed to produce a negative Schick test. His blood likewise failed to show typhoid

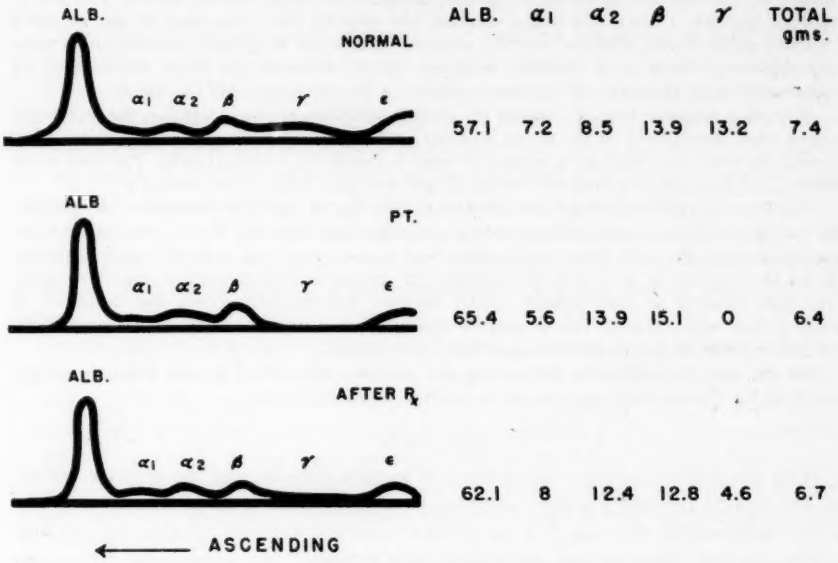

CHART 2. To show normal electrophoretic pattern compared with that of patient before and after giving gamma globulin.

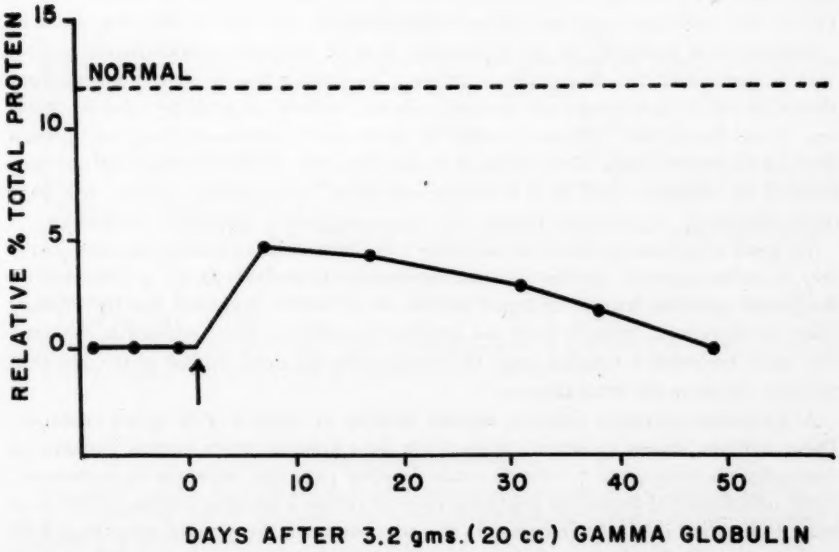

CHART 3. To show gradual decrease of serum gamma globulin as determined by electrophoretic analysis after giving 3.2 gm. gamma globulin subcutaneously.

antibodies following administration of typhoid vaccine in the usual manner. He had a history of epidemic parotitis 3 times. The author observed him only the third time when he had an illness clinically identical with epidemic parotitis, a history of exposure to epidemic parotitis and a white and differential blood count consistent with that disease. However, his serum was negative for complement-fixing antibodies of epidemic parotitis on the 22nd day after the illness.

With this apparent constant inability to produce antibodies it was suggested that one might expect some derangement in the gamma globulin fraction. By electrophoretic analysis of his blood serum, his blood repeatedly gave completely negative results for gamma globulin. The total serum protein and A-G ratio were entirely normal. (Total 6.65 gm., A/G = 1.58, chart 2.)

The absence of gamma globulin gave the most hopeful clue to a possible prophylaxis. Accordingly, he was given subcutaneously immune human serum globulin (Squibb) 20 cc. containing 3.2 gm. gamma globulin. Six days later a surprisingly large amount of gamma globulin was demonstrated in his blood serum by electrophoretic analysis. The gamma globulin content of his blood serum was then followed at approximately weekly intervals for the next 6 wk. and as shown in chart 3 there was a gradual loss to negative results. These surprising results were repeated with the rise in the serum gamma globulin again being demonstrated.

For the past 14 months the patient has had monthly injections of gamma globulin, without benefit of other prophylactic measures, and has suffered no attack of sepsis.

Discussion

With the demonstration of the absence of gamma globulin, and the apparent control of infection by furnishing gamma globulin, there seems little doubt of the existence of a direct relationship in this case. It is not possible to present a proved cause for the defective protein fraction. However, two possibilities seem apparent; (1) a congenital dysfunction in the mechanism of gamma globulin production and (2) an acquired dysfunction in this mechanism. The fact that the patient survived 4½ years and without severe infections appears to make the first unlikely. Although no abnormality has been demonstrated in his liver or reticuloendothelial system, we must assume that a functional abnormality exists if we are to accept the present-day thinking as to the production of immune bodies. Felton[4] has postulated such an acquired dysfunction in man and in mice has produced "immunological paralysis" by an appropriate dose of antigenic polysaccharide. It may then be postulated that this patient's antibody mechanism has by some influence been altered so that it is no longer able to synthesize and/or hold antibody to a specific organism. It was hoped this "influence" could be counteracted permanently by giving gamma globulin; however, there is no evidence to date that the antibody mechanism has been bettered by treatment, and it is therefore anticipated that gamma globulin will have to be continually supplied for control. The latter supports a congenital dysfunction.

To speak of gamma globulin and antibody interchangeably is probably incorrect. However, it seems apparent in this case that pneumococcal antibody is, or is contained in, the gamma globulin fraction of serum protein. It is likewise suggested that the immune bodies of diphtheria, typhoid fever and epidemic parotitis are also contained in this fraction, since no immune reaction could be developed by the usual method in the first two, or by the disease in the latter instance.

A somewhat analogous situation appears to exist in children with lipoid nephrosis. These children, shown by several observers to have lowered serum gamma globulin by electrophoretic analysis,[1, 5, 6] are well known for their particular susceptibility to pneumococcic infections. Of course, in nephrosis there is always a lowered protein as well as a marked alteration in all the fractions. In the case presented, the proteins are normal with the exception of the absence of the gamma fraction. It is suggested that while gamma globulin is present in nephrosis, its occurrence in a lowered amount may be the clue to the increased susceptibility to disease in children with this syndrome.

Summary

A hitherto unrecognized entity manifested by complete absence of gamma globulin with otherwise normal serum proteins and recurrent pneumococcal sepsis is described in an 8 year old male. The patient appears to be normal in other respects and after extensive study no structural or functional change could be demonstrated in any body system although gamma globulin by electrophoretic analysis of his serum was consistently absent. He was unable to produce antibody for the pneumococcus with the four antigenic substances used; a positive Schick test persisted in spite of numerous attempts to reverse it with diphtheria toxoid. No antibody could be demonstrated following administration of typhoid vaccine in the usual manner and his serum was negative for complement-fixing antibodies of epidemic parotitis after he experienced a typical clinical picture of that disease.

Gamma globulin could be demonstrated in his serum after concentrated immune human serum globulin was administered subcutaneously, and its gradual disappearance could be followed by electrophoretic analysis over a period of approximately six weeks. Concurrently, and following the administration of human globulin (3.2 gm. gamma globulin) at monthly intervals, he has been free of pneumococcal sepsis for more than a year, whereas he had experienced clinical sepsis at least 19 times in the previous four years in which eight different types of pneumococci had been recovered from blood culture during 10 different episodes.

It is postulated that by some acquired "influence" the patient's antibody mechanism has been altered so that he is no longer able to synthesize and/or hold antibody to a specific organism. A complete defect of plasma proteins cannot be excluded.

This case, in addition to its uniqueness, suggests many possibilities for study of possible control and treatment of disease with gamma globulin.

Acknowledgment

Appreciation is due Dr. Monroe Romansky for his suggestions and Miss Pearl Anderson for her technical assistance in the electrophoretic analyses.

References

1. Stern, K. G., and Reiner, M., Electrophoresis in medicine, Yale J. Biol. & Med. **19**:67, 1946.
2. Schick, B., and Greenbaum, J. W., Edema with hypoproteinemia due to congenital defect in protein formation, J. Pediat. **47**:241, 1945.
3. Krebs, E. G., Depression of gamma globulin in hypoproteinemia due to malnutrition, J. Lab. & Clin. Med. **31**:85, 1946.
4. Felton, L. D., Significance of antigen in animal tissues, J. Immunol. **61**:107, 1949.
5. Longsworth, L. G., and MacInnes, D. A., Electrophoretic study of nephrotic sera and urine, J. Exper. Med. **71**:77, 1940.
6. Farnsworth, E. B., and Ruppenthal, N. C., Electrophoretic studies on serum and urine proteins in nephrosis treated with ACTH, J. Lab. & Clin. Med. **38**:407, 1951.

Spanish Abstract

Agammaglobulinemia

Aun cuando existen casos reportados en la literatura con hipoproteinemia y ausencia casi completa de gammaglobulina, este es el primero que se publica con ausencia completa de gammaglobulina y proteínas totales normales.

Se trata de un niño de 8 años cuyos padecimiento se manifiesta hasta los 4½. Se inicia con escalofrío, fiebre y dolor intenso en la rodilla izquierda, 16.400 leucocitos con 88% de neutrófilos. Cura con penicilina y permanece bien por 2 semanas para recaer con una infección respiratoria

superior que terminó con neumonía y con parotiditis izquierda. Después de estar 10 días bien, presenta cuadro de vómitos y fiebre intensa, que se repite unos días mas tarde, permaneciendo febril por dos semanas cuando comienza con otalgia. Se alivia con sulfa que se administra por dos semanas pero al suspenderla recidiva la fiebre y así sucesivamente continúa con infección tras infección incluyendo 19 episodios de septicemia en 10 de los cuales se aisló de su sangre varios tipos de neumococos.

El niño fué estudiado detenidamente y cada uno de sus aparatos y sistemas fué examinado por especialistas auxiliados por todos los exámenes de laboratorio que se creyeron pertinentes sin encontrar la explicación de sus infecciones tan frecuente. La administración de penicilina inmediatamente después de iniciarse escalofrio y fiebre y aún más, la administración profiláctica de sulfadiazina, no dió resultados satisfactorios pues aún bajo esta última el niño desarrollo 6 septisemias en tres de las cuales el hemocultivo aisló neumococos.

Se pensó entonces que seguramente no formaba anticuerpos antineumocócicos y se prepararon y administraron varias vacunas autógenas con número creciente de distintos tipos de neumococos sin encontrarse anticuerpos en su sangre y finalmente se hizo la vacunación con polisacáridos neumocócicos con iguales resultados llegándose a la conclusión de que seguramente el organismo del niño no formaba anticuerpos para ningún germen y trató de comprobarse dicha posibilidad. Efectivamente, así sucedió, pues el paciente no presento schick negativo después de vacunación adecuada, ni anticuerpos antitifóidicos ni para la parotiditis, la cual la presentó en 3 ocasiones.

Lógico era entonces suponer alguna anormalidad de su fracción gammaglobulina confirmándose por el examen electroferético en repetidas ocasiones que su suero sanguíneo no contenía en absoluto globulina-gamma aunque sus proteínas totales y el cociente A/G eran completamente normales.

Este hecho hacía esperar resultados satisfactorios con el uso profiláctico de seroglobulina humana y se le administraron 20 c.c. de un preparado comercial (Squibb) conteniendo 3.2 gms. de gammaglobulina demostrándose su presencia en el suero seis días después y desapareciendo paulatinamente dentro de las seis semanas siguientes. En los últimos 14 meses el enfermo no ha tenido ningun cuadro septisémico y ha sido tratado exclusivamente con inyecciones mensuales de globulina gamma.

Se postula que puesto que el cuadro del enfermo se inició a los 4½ años, el mecanismo de producción de anticuerpos fué alterado por algun "factor" adquirido y ya no fué capaz de sintetizar o conservar anticuerpos en contra de cualquier germen.

El caso ilustra magistralmente la correlación entre la ausencia de gammaglobulina y el desarrollo frecuente de procesos infecciosos y viceversa y aunque quizás sea incorrecto hablar indistintamente de gammaglobulina y anticuerpos, como parece probarse por este caso, es casi seguro que los anticuerpos antineumocócicos, antidiftérico, tifóidico y de la parotiditis se encuentran en esta fracción de las globulinas humanas.

Asímismo, los autores sugieren que en situaciones análogas de gammaglobulina disminuída como en la nefrosis lipóidica, la susceptibilidad a la infección pueda explicarse sobre bases semejantes.

Walter Reed Army Medical Center

IDIOPATHIC HYPOPROTEINEMIA

Report of a Case of Transient Edema, Depression of Plasma Albumin and Gamma Globulin and Eosinophilia

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A 3½ year old boy with a rather unique syndrome of edema, hypoproteinemia without proteinuria, and eosinophilia has been observed. Electrophoretic analysis of the plasma proteins revealed a considerable decrease in albumin and gamma globulin, and a slight elevation of the alpha globulins. Although the history suggested acute glomerulonephritis, this diagnosis was untenable in the absence of confirmatory clinical and laboratory findings. Recovery was uneventful, and total and fractional serum protein values had returned to normal 10 weeks after the onset of the illness.

CASE REPORT

R. D., a 3 yr., 5 mo. old Negro boy, was admitted to the Children's Medical Service† because of swelling of the eyelids, abdomen and legs of 10 or 12 days' duration.

The child's past history was uneventful except that since age 2 he had had recurrent tonsillitis. His diet had been adequate since birth.

Four weeks before admission he contracted a mild upper respiratory infection lasting about 1 wk. He then was well until 2 wk. before admission when symptoms recurred. This time the cough was more severe, and was associated with vomiting once or twice daily. The boy's mother observed that the patient voided only about twice daily, the urine passed being darker than usual. He complained of increased thirst, though his actual fluid intake was not known. Ten to 12 days before entry mild morning periorbital edema was observed and his shoes were found to fit unusually tightly.

Eight days before entry the patient's physician made a diagnosis of acute tonsillitis. A sulfonamide was prescribed though only 3 tablets were taken. In a few days the cough was gone. The boy's mother noted that he was fatigued and heavier than usual, but no weights were obtained. Mild anorexia was present and oliguria persisted.

Four days before entry the boy developed moderate swelling of his legs and abdomen. The leg edema subsided slightly while the abdominal swelling progressed. The day before entry the patient was again seen by his physician who suspected acute nephritis. However, there was no fever and a urinalysis showed no albumin.

The family history revealed that the mother had had asthma and hay fever. No family member ever had had renal disease or edema in any form.

The physical examination at the time of admission to the hospital showed the patient to be a well nourished, alert, Negro boy, manifesting periorbital puffiness, moderate ascites, and edema of the legs. The temperature was 37.8°C., rectally, and the blood pressure was 90/60 mm. The boy's height was 102 cm. and his weight 17.9 kg. Both in height and weight (normally approximately 15.9 kg.), the patient surpassed 75% of children his age. The tonsils were hypertrophic and en-

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TABLE 1

Clinical and Laboratory Data

Day of Observation 1949	1 (1/25)	2	3	4	5	6	7	8	9	10	11	12	13	14	21	64 (3/29)	125 (6/7)	126	127	143
Urinalysis																				
Protein	0	0	0	0	—	0	—	—	—	0	—	—	—	—	0	0	0	0	—	0
Sediment	0	0	0	0	—	0	—	—	—	0	—	—	—	—	0	0	0	occ. wbc	—	rare wbc
Specific Gravity	1.018	1.010	1.014	1.017	—	1.008	—	—	—	1.019	—	—	—	—	1.016	1.028	1.005	1.030	—	1.025
Hemoglobin	12.2	—	—	13.3	—	—	—	—	—	—	—	—	—	—	—	11.7	12.0	12.6	11.1	—
Sedimentation Rate	3	4	—	—	—	—	—	—	—	—	—	—	—	—	—	21	—	—	—	—
Eosinophil Count	—	703	568	—	719	—	813	—	—	—	—	—	—	—	381	222	—	—	—	—
NPN	17	—	—	—	—	—	—	16	—	—	—	—	—	15	47	18	—	—	—	18
Serum Protein	3.14	—	—	—	—	—	—	4.60	—	4.60	—	—	—	5.18	6.78	6.48	—	—	6.20	6.53
Albumin*	2.37	—	—	—	—	—	—	2.84	—	2.80	—	—	—	3.66	—	4.60	—	—	—	4.39
Globulin	0.77	—	—	—	—	—	—	1.76	—	1.80	—	—	—	1.52	—	1.88	—	—	—	2.14
Blood Pressure	90/60	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	88/45	—	—	—
Weight (kg.)	17.9	17.9	17.0	17.0	16.3	16.0	16.1	15.7	15.8	15.3	15.4	15.6	15.8	—	16.5	17.0	—	—	—	—
Fluid Intake	280‡	—	1160	1060	—	1320	1110	1270	660	1020	1180	1800	—	—	—	—	—	—	—	—
Urine Output†	120	—	1340	1160	—	800	385	835	430	900	650	400	—	—	—	—	—	—	—	—

* Normal values[1] for a 3 yr. old child are 4.70± 0.32 gm. albumin and 1.80± 0.34 gm. globulin/100 cc. serum; for a 4 yr. old, 4.70± 0.32 gm. albumin and 2.03± 0.34 gm. globulin.[2]

† Accuracy limited by occasional incontinence.

‡ Six hour period.

larged about 3 times their normal size, but they were not acutely inflamed. A few anterior cervical lymph nodes were palpable; there was no other adenopathy. The lungs were clear. The heart was normal. The abdomen was slightly protuberant with shifting dulness to percussion. Liver and spleen were not palpable. The genitalia were not remarkable. The extremities revealed a 2+ pitting edema of both feet and legs, extending into the thighs.

Laboratory data (table 1): The initial urine was straw-colored with a pH of 6.5 and a specific gravity of 1.018. No albumin (heat and acetic acid test), sugar or formed elements were found. A WBC count was 7.5 thousand/cmm. A second count was 10.6 thousand/cmm. with 38% polymorphonuclear leukocytes, 52% lymphocytes, 4% monocytes and 6% eosinophils. A direct eosinophil count was 793/cmm. Hgb. was 12.2 gm./100 cc. (Evelyn photelometer), and the erythrocytes and platelets were normal on smear. The sedimentation rate (Westergren) was 3 and 4 mm./hr. on 2 occasions. The total serum proteins measured 3.14 gm./100 cc., of which 2.37 gm. were albumin and 0.77 gm. globulin, as determined by the Howe method.* The serum NPN was 17 mg. and the cholesterol 182 mg./100 cc. The Hinton test for syphilis was negative on 2 occasions. A throat culture revealed no beta hemolytic streptococci. Roentgenographic examination revealed the chest to be normal, but an abdominal film showed a generalized ground-glass haziness consistent with ascites.

Over the next 12 days several urinalyses were done (table 1), none of which revealed any albumin or abnormalities of the sediment. The specific gravity ranged from 1.008 to 1.019, and the pH from 6.5 to 8.5. The determinations of Hgb., sedimentation rate, NPN, serum protein, albumin, globulin and circulating eosinophils are listed in table 1. On the fourth day of hospitalization the serum sodium was 138.7 mEq./l., chloride 105 mEq./l., carbon dioxide content 27.1 mEq./l., calcium 8.6 mg./100 cc., inorganic phosphorous 4.7 mg./100 cc. and alkaline phosphatase 4.7 Bodansky units/100 cc. The thymol and cephalin flocculation tests were negative, and a prothrombin time was normal.

On the eighth day a urea clearance test and a bromsulfalein test were normal. An ECG was normal. Intradermal tuberculin tests were negative even at a dilution of 1:100. A trichinella skin test was also negative, 7 days after entry.

Course: The patient was restricted to bed and was given a diet containing less than 1 gm. salt/day, the protein initially being limited to 1 gm./kg./day. The patient's temperature became normal on the second day. There was a modest spontaneous diuresis reaching 1340 cc. on his third day. His output thereafter averaged about 600 cc. daily. He lost weight and edema steadily (table 1).

Seven days after entry the boy developed an acute pharyngitis with a fever of 39.5°C. orally and a leukocytosis of 22.5 thousand cells/cmm. He responded quickly to intramuscular penicillin. A throat culture taken prior to treatment and a chest RG were normal.

By the tenth day the patient's weight had decreased from 17.9 to 15.3 kg. His serum proteins were now 4.60 gm./100 cc., and he no longer had any detectable edema. Serum for the first electrophoretic pattern was drawn this day. The temperature and a WBC count were normal and 48 hr. later he was discharged.

One week later he was seen in the Children's Medical Out-Patient Department, where he was found to be normal except for hypertrophic tonsils. His circulating eosinophils were 381/cmm. Six weeks later they were 222/cmm. At this time serum for the second electrophoretic pattern was obtained. An adenotonsillectomy was performed.

The patient was last seen 1½ yr. later. He had developed mild asthma but was otherwise well. He weighed 17.4 kg. and had a blood pressure of 92/60. Urinalysis was normal and his eosinophil count was 640/cmm. A final check of his electrophoretic pattern was made.

The results of serial determinations of total serum protein and fractionation both by the Howe method and by electrophoresis are shown in table 2. At the time of admission to the hospital the serum protein deficiency was characterized by moderate lowering of the albumin fraction and profound lowering of the globulin fraction as determined by the Howe method. A week later a rise in total serum protein had taken place resulting from increases of 0.47 and 0.99 gm./100 cc., respectively, in albumin and globulin. Normal total protein values were found at the end of 3 wk. and normal fractionation by the Howe method 6 wk. later and in all subsequent determinations.

Electrophoretic patterns showed initially marked depression of the albumin and of the gamma

* The "albumin" by the Howe[2] method includes most of the α-1 and α-2 globulins.

TABLE 2

ELECTROPHORETIC STUDIES OF SERUM PROTEINS

	2-3-49*		3-29-49		1-4-51	Normal Average Values in This Laboratory			
	%	gm./100 cc.	%	gm./100 cc.	%	%		gm./100 cc.	
						Serum	Plasma	Serum	Plasma
Total Protein†		4.6		6.5				6.8	7.1
Albumin†		2.8		4.8					
Globulin†		1.8		1.7					
Albumin	39.9	1.84	50.9	3.30	57.4	55	53	3.74	3.76
Alpha-1	10.2	0.47	5.7	0.37	4.7	5	5	0.34	0.36
Alpha-2	18.8	0.86	13.1	0.85	11.0	10	10	0.68	0.71
Beta-1	20.7	0.95	18.5	1.20	15.8	15	14	1.02	0.99
Beta-2	6.0	0.28	2.1	0.14	3.1	4	4	0.27	0.28
Fibrinogen			—	—	—	—	4	—	0.28
Gamma	4.3	0.20	9.7	0.63	8.1	11	10	0.75	0.71

* Plasma determination.

† Howe method. [2]

globulin fractions with slight elevation of the values for alpha-1 and alpha-2 globulin. These abnormalities of the electrophoretic pattern disappeared concomitantly with those observed by Howe fractionation.

DISCUSSION

This case is a diagnostic problem which apparently represents an unusual transient derangement of plasma protein metabolism. The chief entities simulated by this boy's illness are acute glomerulonephritis without proteinuria, nephrosis, a reaction of the serum sickness type, and idiopathic hypoproteinemia.

Acute glomerulonephritis, through strongly suggested by the history, was not substantiated by clinical and laboratory findings. The syndrome of "acute glomerulonephritis without proteinuria or non-protein nitrogen retention"[3-5] was considered, but in the cases which have been described some other typical features of acute nephritis have been present such as hypertension[3-5] or minimal hematuria.[4] Also, in acute nephritis, eosinophilia is somewhat uncommon[6] and the electrophoretic pattern usually reveals an absolute increase in gamma globulin and normal alpha globulins.[7] The electrophoretic pattern in the patient reported here revealed depressed albumin, strikingly depressed gamma globulin and increased alpha globulins, a pattern somewhat suggestive of nephrosis.[7] This diagnosis is, however, untenable in the absence of proteinuria, and there was also no evidence of the hypercholesteremia and absolute hyperfibrinogenemia generally present in this syndrome.[8]

There are several factors such as the eosinophilia and the fever to suggest a hypersensitivity state. In that case capillary injury might have caused the edema, and the hypoproteinemia would have been secondary to the development of edema. However, the fact that the edema gradually increased in severity would favor the interpretation that the hypoproteinemia was primary and the edema secondary. In view of the decrease in serum albumin and gamma globulin it might be argued that capillary injury permitted escape of only the smaller protein molecules into the interstitial fluid. However, in one study

directly relating to the differential permeability of capillaries to plasma proteins it was found that such probably did not exist; for in this study the electrophoretic pattern of pemphigus blister fluid reflected closely the plasma alterations.[9] Also, evidence that edema fluid in acute nephritis contains very little protein[10] challenges the concept that capillary permeability to proteins is commonly abnormal in acute nephritis[11] and in nephritis without proteinuria.

In the present case it would appear that the hypoproteinemia was due to some obscure disturbance of the albumin and gamma globulin (and possibly fibrinogen) metabolism, either increased destruction, as in the patient studied by Albright, Bartter and Forbes,[12] or diminished production. This case may be related to the poorly understood group of idiopathic hypoproteinemias. Seven convincing cases of this syndrome have been reported in adults,[12-17] all but two[12,14] occurring in women. One patient had experienced an earlier unexplained transient edema[16] and two others manifested moderate eosinophilia.[13,17] Certain other cases of unexplained hypoproteinemia appear to be secondary rather than idiopathic.[15,18,19] In the one adult case which had been studied by electrophoresis the various plasma fractions were decreased to a similar degree, the gamma globulin showing the least decrease.[13] Two cases of edema and unexplained hypoproteinemia in children have been reported.[20,21] In one the defect appeared to be congenital, and this patient had a family history of hypoproteinemia.[20] Both children were found to have a virtual absence of gamma globulins by electrophoresis. In several patients with idiopathic hypoproteinemia high protein diets had no effect on the serum protein levels.[13,15,20] However, in one instance of starvation hypoproteinemia in which there was a marked depression of gamma globulin,[22] high protein feedings were followed by gradual regeneration of all plasma fractions, the gamma globulin rising from 0.16 to 0.68 gm./100 cc. in nine weeks. This rate of gamma globulin regeneration closely approximates that seen in the patient reported here.

The patient reported in this paper thus seems to occupy a unique position among those rare instances of inexplicable hypoproteinemia. The defect probably is one of transient derangement of plasma albumin and gamma globulin metabolism. It is impossible to determine from the available data whether increased destruction or diminished production accounted for the deficiency. It is possible that this patient's illness is related pathogenetically to acute glomerular nephritis or to nephrosis. Because of the fact that renal defects differ in the two conditions only quantitatively rather than qualitatively, certain investigators prefer to regard these as varying manifestations of one disease process. In both, diminished protein production has been suspected to occur.[23,24] Hypersensitivity factors have long been postulated in acute nephritis.

Summary

A 3½ year old Negro boy with an obscure syndrome of inexplicable, transient, acquired hypoproteinemia, involving plasma albumin and especially gamma globulin, has been observed. Edema, oliguria and weight gain were noted 10 days following an attack of acute tonsillitis. Hypertension, renal impairment, proteinuria and hematuria were conspicuously absent, and an associated eosinophilia subsided as recovery progressed. Plasma protein regeneration was complete in 10 weeks. The patient has since developed mild asthma but has otherwise remained well.

This appears to be an unusual case of transient derangement of plasma protein

metabolism. Possible relationships to the syndromes of acute nephritis without proteinuria, nephrosis, serum sickness and idiopathic acquired hypoproteinemia are discussed.

REFERENCES

1. Trevarrow, V., Kaser, M., Patterson, J. P., and Hill, R. M., Plasma albumin, globulin and fibrinogen in healthy individuals from birth to adulthood, J. Lab. & Clin. Med. **27**:471, 1942.
2. Howe, P. E., Use of sodium sulfate as globulin precipitant in determination of proteins in blood, J. Biol. Chem. **49**:93, 1921.
3. Keefer, C. S., Late non-suppurative disorders of hemolytic streptococcal diseases, Texas State J. Med. **35**:457, 1939.
4. Poe, W. D., and Alsobrook, W. L., Extra-renal manifestations of acute glomerulonephritis, J. Bowman Gray School M. Wake Forrest Coll. **2**:105, 1944.
5. Crofton, J., and Truelove, W., Apparent acute glomerulonephritis without albuminuria, Lancet **2**:54, 1948.
6. Kollert, V., and Paschkis, K., Das weisse Blutbild bei Nephritis, Ztschr. f. klin. Med. **112**:275, 1930.
7. Luetscher, J. A., Jr., Biological and medical applications of electrophoresis, Physiol. Rev. **27**:621, 1947.
8. Malmros, H., and Blix, G., Plasma protein in cases with high erythrocyte sedimentation rate, Acta med. Scandinav. (Supp.) **170**:280, 1946.
9. Lever, W. F., Proteins in pemphigua vulgaris. II. Electrophoretic analysis of proteins in blister fluid of patients with pemphigus vulgaris, J. Invest. Dermat. **14**:219, 1950.
10. Warren, J. V., and Stead, E. A., Protein content of edema fluid in patients with acute glomerulonephritis, Am. J. M. Sc. **208**:618, 1944.
11. Fishberg, A. M., Hypertension and Nephritis, ed. 4, Philadelphia, Lea & Febiger, 1939, p. 453.
12. Albright, F., Bartter, F., and Forbes, A., Fate of human serum albumin administered intravenously to patient with idiopathic hypoalbuminemia and hypoglobulinemia, Tr. A. Am. Phys. **62**:204, 1949.
13. Rytand, D. A., Edema with unexplained hypoproteinemia, Arch. Int. Med. **69**:251, 1942.
14. Cope, C. L., and Goadby, H. K., Study of case of idiopathic hypoproteinemia, Lancet **1**:1038, 1935.
15. Binger, M. W., and Keith, N. M., Generalized edema of indeterminate etiology: Report of three cases, J. A. M. A. **109**:1, 1937.
16. Johansen, A. H., Hypoproteinemia, Acta path. et microbiol. Scandinav. (Supp.) **37**:272, 1938.
17. Messinger, M. J., Generalized edema associated with hypoproteinemia, Canad. M. A. J. **55**:381, 1946.
18. Thompson, W. H., McQuarrie, I., and Bell, E. T., Edema associated with hypogenesis of serum proteins and atrophic changes in liver, J. Pediat. **9**:604, 1936.
19. Myers, W. K., and Taylor, F. H. L., Hypoproteinemia probably due to deficient formation of plasma proteins, J. A. M. A. **101**:198, 1933.
20. Schick, B., and Greenbaum, J. W., Edema and hypoproteinemia due to congenital defect in protein formation, J. Pediat. **27**:241, 1945.
21. Stern, K. G., and Reiner, M., Electrophoresis in medicine, Yale J. Biol. & Med. **19**:67, 1946.
22. Krebs, E. G., Depression of gamma globulin in hypoproteinemia due to malnutrition, J. Lab. & Clin. Med. **31**:85, 1946.
23. Addis, T., Glomerular nephritis, diagnosis and treatment, New York, MacMillan Company, 1948, p. 215.
24. Fishberg,[11] p. 145.

SPANISH ABSTRACT

Hipoproteinemia Idiopática

Reporte de un Caso de Edema Transitorio, Disminución de la Albúmina y Gammaglobulina del Plasma, y Eosinofilia

Se trata de un niño negro de 3 años cinco meses que se internó en el Hospital con historia de 4 semanas antes, iniciada con una infección respiratoria superior ligera que duró cerca de una semana. Permaneció sano la siguiente, terminando la cual recayó con tos más severa y vómitos, orina escasa y

obscura, y sed; dos días más tarde apareció edema periorbitario moderado y cuatro días antes de admitirlo, edema de las piernas y abdomen haciéndose el diagnóstico de nefritis aguda. Al examen físico se ratificaron los datos de edema de los párpados, miembros inferiores, ligera ascitis, y amígdalas francamente hipertrofiadas pero no inflamadas en forma aguda.

Los exámenes de laboratorio demostraron: orina con pH de 6.5 a 8.5, densidad de 1.008 a 1.019, ausencia de albúmina continuadamente, eosinofilia sanguínea de 636 eosinófilos por m.m. cúbico. Fórmula roja, sedimentación eritrocítica, plaquetas, colesterol, y nitrófeno no proteíco fueron normales. Exudado faríngeo negativo para estreptococo hemolítico beta. Las pruebas de timol, floculación de la cefalina, protrombina, depuración ureica y bromosulfaleina fueron también normales.

El mantoux y las cutireacciones para la triquina también fueron negativas. P.A. 90/60.

El enfermo mejoró progresivamente con reposo en cama y dieta con menos de 1 gr. de sal y 1 gr. de proteínas por Kg. de peso y por día, no obstante un episodio febril por faringitis aguda, que respondió rápidamente a la penicilina. El edema desapareció gradualmente y 10 días después de admitido fué dado de alta completamente libre de él.

El patrón de sus proteínas es muy importante; al admitirlo tenía 3.14 grs./100 c.c. de proteínas totales, de las cuales 2.37 grs. eran de albúmina y 0.77 grs. de globulinas (Método de Howe). Por el método de electroforesis se encontró disminución marcada de la albúmina y de la gammaglobulina con elevación ligera de las globulinas alpha 1 y alpha 2. (por el método de Howe estas globulinas están incluídas en la dosificación de la albúmina). A las 3 semanas las proteínas totales eran normales y a las 6 semanas las globulinas fraccionadas también se hicieron normales. Su cuenta total de eosinófilos en esta época fué de 222 por m.m. cúbico.

El niño fué visto un año más tarde, había presentado ataques de asma de ligera intensidad, su orina era normal y tenía una cuenta total de eosinófilos de 640 por m.m. cúbico.

La discusión diagnóstica del caso lleva a la conclusión de que probablemente se trató de una alteración transitoria del metabolismo de las proteínas plasmáticas. Efectivamente fué posible eliminar una glomerulonefritis clásica por la clínica y el laboratorio; importantes de considerar a este respecto, además de otros datos, la eosinofilia que es rara en la nefritis aguda, y la ausencia de aumento de la gammaglobulina y globulinas alpha normales que es un hallazgo frecuente en las glomerulonefritis. El cuadro de glomerulonefritis sin proteinuria y sin retención de nitrógeno no proteíco puede también eliminarse entre otras cosas por la falta de hipertensión y hematuria. En realidad, el patrón proteico del enfermo era más sugestivo de una nefrosis, sin embargo, es imposible sostenerla por la ausencia de albuminuria, hipercolesterolemia e hiperfibrinogenemia generalmente presentes en este síndrome.

Que el caso sugiere un estado de hipersensibilidad esta respaldado, entre otros factores, por la eosinofilia y la fiebre. Podría entonces sospecharse que el edema fuera causado por lesión capilar pero su aumento gradual está en contra y es mas lógico aceptar que es secundario a la hipoproteinemia la cual parece ser de naturaleza primaria. Además, estudios recientes han demostrado que probablemente no existe permeabilidad selectiva de la pared capilar a las distintas proteínas plasmáticas, de manera de dejar pasar las de molécula pequeña; y por otra parte, la comprobación de que el líquido del edema nefrítico contiene muy pocas proteínas, sugiere que el edema del enfermo no tenga otra explicación que la hipoproteinemia siendo imposible saber si esta fué por déficit en su formación o destrucción excesiva.

Existen 7 casos publicados en la literatura del síndrome de hipoproteinemia idiopática en adultos, 5 eran mujeres, 1 tuvo un edema transitorio inexplicable y en otros 2 eosinofilia moderada, en algunos la hipoproteinemia parece ser mas bien secundaria que primaria. En niños, dos casos se han publicado, uno con historia en la familia de hipoproteinemia y su defecto fué congénito, en ambos había ausencia casi completa de gammaglobulinas. A menos que la disminución de globulina gamma sea por desnutrición su regeneración no se logra con alimentación proteíca.

En conclusión, es posible que el síndrome este relacionado patogenéticamente con la nefritis aguda glomerular o con la nefrosis ya que la lesión renal difiere solo cuantitativamente en ambas entidades y pueden aceptarse como manifestaciones distintas de un solo proceso patológico, en el cual se sospecha que haya disminución en la producción de proteínas y que; en la nefritis aguda, la posibilidad de un factor de hipersensibilidad juegue algún papel de importancia.

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STUDIES OF THE IMMUNOLOGY OF THE NEWBORN INFANT

1. Age and Antibody Production

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THE successful active immunization of the very young infant is of great importance to the pediatrician. Yet many separate factors are involved in the immune response of the newborn. The following studies represent an attempt to separate and study independently such factors as: the relation between the age of an infant and his ability to produce antibody; the effect of circulating antibody on active immunization; the transplacental transfer of antibody from mother to infant; and the differences between different antigen-antibody systems. In order to hold constant as many of the variables as possible, the authors have studied in detail a single antigen- antibody system (diphtheria) for which accurate quantitative technics are available, and in less detail for purposes of comparison a second system (tetanus) for which methods are as accurate.

AGE AND ANTIBODY PRODUCTION

A large and useful part of the data bearing on the immunology of the newborn infant has come from clinical studies of immunizing schedules. There have been many careful reviews of this subject,[1-3] the most recent being that of Peterson and Christie.[3] But with the notable exception of the recent careful work of Vahlquist,[4,5] quantitative interpretation of these studies and separation of the factors involved has often been difficult for reasons such as the following:

1. Antigen-antibody reactions may have been used for which there were no accurate methods of titration. Only rough, qualitative conclusions could be drawn.

2. Some studies used antigen-antibody reactions that require complement. The blood of the newborn infant has a low level of complement. This may have caused an undetermined error in the antibody estimation.

3. Particularly in the older literature, the authors may not have recognized the interference with active immunization by passive circulating antibody derived transplacentally from the mother.

4. More recently, several studies[3, 6-9] have measured the effect of a series of injections given at approximately monthly intervals. In these studies, the immunization course was not completed until the infant was a few months old, so that information concerning the first weeks of life is lacking. Furthermore, the antibody titer measured at the end of the series of injections is the sum of the response to the primary immunization and the responses to the "booster" injections. Interpretation is also complicated by the fact that as a rule the second or third injections were given without knowing the titer of circulating antibody

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resulting from the first injection, although circulating antibody may interfere with reaction to subsequent injections of antigen. Difficulties such as these have tended to limit the conclusions that could be drawn about the direct relation of age to immune response.

In the present study the authors have tried to avoid these difficulties by the serial study of the responses of infants to a single injection of high titer diphtheria or tetanus toxoids (adsorbed on alum) using only infants who had no circulating antitoxin at the time of immunization. The diphtheria and tetanus systems were chosen because of the relative accuracy of methods for measuring their antitoxins.

This study was designed to study quantitatively the antibody response of the newborn. It must not be construed as a study of a proposed clinical immunization schedule.

Materials and Methods

Diphtheria Antigen: A highly purified diphtheria toxoid specially prepared by Lederle Laboratories, and adsorbed onto alum,[10] containing 100 Lf toxoid/0.5 cc. immunizing dose. The same lot of alum-adsorbed toxoid was used throughout the study.

Antitoxin Titrations: The serum neutralization technic described by Fraser[11] was used throughout. In this method, varying dilutions of serum are mixed with a known amount of toxin and injected into the skin of a rabbit. A reaction at the site of injection indicates excess of toxin over antitoxin. The lowest level routinely tested for was .002 units/cc. Infant blood specimens were allowed to clot, the serum was separated by centrifuge, and stored in the ice box (not frozen) after the addition of a small amount of merthiolate. Antitoxin content was measured as soon as possible after collection.

Tetanus: For that portion of the work in which the response to tetanus toxoid was studied, a highly purified tetanus toxoid was kindly supplied by Dr. Louis Pillemer. This was adsorbed onto the same batch of alum used for the diphtheria and used in a concentration of 163 Lf toxoid/0.5 cc. immunizing dose.

Titrations of tetanus toxoid were kindly carried out by the staff of the Lederle Laboratories by a mouse protection technic modified from the N.I.H. procedure.

Schick-Testing: Infants were not routinely Schick-tested. A few Schick tests were performed but only at exactly the time of administration of the immunizing diphtheria toxoid, so as to eliminate for practical purposes the antigenic effect of the Schick test toxin.

Selection of Patients: This work was made possible by the close cooperation of the New York Foundling Hospital. This hospital is unusually well suited to this type of investigation, because it cares for a large number of normal infants of ages up to about 2 yr. Most of these infants are awaiting adoption or other disposition and are not ill. Many can be followed for over 6 mo.

Selection of patients for the different age-groups was largely on the basis of practicality. Infants who were expected to leave the hospital early were more likely to be placed in the younger age-groups. Infants who were known to be involved in prolonged litigation or who were for other reasons expected to stay for a longer period were more likely to be placed in the older age-groups. Only normal infants were used in the study.

This type of selection is not ideal, in that it might be argued that infants known to be going out for early adoption might constitute a different mass of material from infants for whom disposition could not easily be found. However, the factors determining length of stay at the hospital are manifold and usually unrelated to the infant's own characteristics, so that selectional bias of this type is not a major danger.

Procedure: Infants at New York Foundling Hospital selected for inclusion in the study were numbered and assigned to specific age-groups. Usually an initial blood specimen was obtained as early as possible in life, and when possible a sample of maternal blood. At the time of immunization for a particular age-group, another blood sample was obtained and the immunizing dose of 100 Lf diphtheria toxoid on alum in 0.5 cc. volume was injected subcutaneously in the deltoid region. Follow-up blood specimens were usually obtained 1 wk., 2 wk., 1 mo., 2 mo., 3 or 4 mo. and 6 mo. after immunization. Although many infants or particular blood specimens were of necessity lost from the study some time during the 6 mo.' follow-up, full follow-up was obtained on many.

Definition of Age-Groups: Infants under 2 wk. of age: This includes infants through the 14th day of life. Most of these infants were between 7 and 14 days old when immunized.

One Month of Age: All infants in this age-group were over 4 and less than 5½ wk. of age when injected.

Two to Four Months of Age: Includes all infants whose age at time of injection was more than 11 wk. and less than 18 wk.

Six Months of Age: All infants over 26 wk. and under 36 wk. of age, but including one infant immunized at 21 wk. of age.

Results

Forty infants were immunized. These infants had no evidence of passive transplacental circulating antitoxin at the time of immunization. None showed antitoxin at the lowest level tested for (.002 U./cc.) in the first blood specimen, and in all cases where the

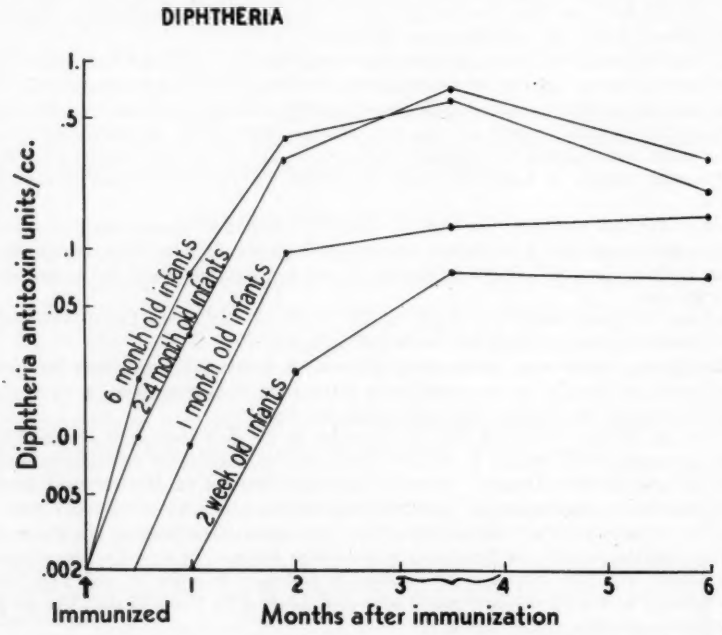

Chart 1. Diphtheria immunization: Mean response of infants of different age groups. Antitoxin titer is graphed on logarithmic scale.

mother's blood could be obtained, it also showed no antitoxin. Eleven infants were under 2 weeks of age. Ten were 1 month old, 10 between 2 and 4 months, and 9 were 6 months old.

The antitoxin responses of these four groups of infants to the single immunization are summarized in chart 1. This is a graph of the mean antitoxin titer of all infants in each age-group at each time-period after immunization. (In the calculation of mean titers for this graph antitoxin titers of less than .002 were treated as if zero. This introduces a small error whose limits are defined in table 1.)

It is clear from inspection of chart 1 that the young infants did not respond as quickly with production of antibody as did the older infants. This agrees with the results of

TABLE 1

ANTITOXIN RESPONSE IN u./cc. SERUM OF INFANTS OF DIFFERENT AGES TO SINGLE INJECTION OF 100 Lf DIPHTHERIA TOXOID (ALUM PPT.). ANTITOXIN RESPONSE IS GIVEN AS MEAN LEVEL, ± STANDARD ERROR OF MEAN.

Age at Time of Immunization	Time After Immunization									
	2 Wk.		1 Mo.		2 Mo.		3–4 Mo.		6 Mo.	
	No. of Cases	Antitoxin* Level	No. of Cases	Antitoxin* Level	No. of Cases	Antitoxin Level	No. of Cases	Antitoxin Level	No. of Cases	Antitoxin Level
2 wk.	11	0, .001	11	.002, .003	8	.023± .012	5	.076± .015	5	.074± .016
1 mo.	10	0, .001	10	.009, .0095	8	.098± .020	3	.133± .033	4	.150± .018
2–4 mo.	9	.011, .012	9	.035, .035	10	.300± .084	9	.728± .245	9	.294± .052
6 mo.	8	.021, .022	10	.073, .073	7	.393± .129	4	.625± .216	3	.200± .029

* The lower of 2 values given in these columns was calculated assuming that $<.002=0$. The higher value was calculated assuming that $<.002=.001$.

Vahlquist.[4,5] However in contrast to his work, the present data also shows that the younger infants never did reach the antitoxin levels which the older infants achieved. Vahlquist, using a much less potent antigen (40 Lf. toxoid on alum), had found that even the younger infants eventually reached the same average levels as the older ones. But because of his smaller dose of antigen, the responses of all his infants were in general well below those in this study.

The antitoxin responses of the infants under 2 weeks of age are clearly much below those of the one month old infants. Also the responses of the one month old infants are well below those of the two month old. But there is no great difference between the responses of infants 2 to 4 months old and those of infants 6 months old.

(A group of premature infants now being studied will be reported on in a subsequent paper. Their antitoxin response appears to be considerably less than that of this group of newborn infants under 2 weeks of age.)

STATISTICAL EVALUATION

The differences in chart 1 between the response of infants under 2 weeks of age and of those one month of age, and between the one month old infants and those 2 months and over can be shown to be statistically significant at the 5% level for all time periods except 3 to 4 months after immunization (when the number of cases is too small).

The first detectable antitoxin (.002 U./cc. or above) appeared two weeks after immunization in one infant 3 months of age, and in five infants 6 months of age. No infant under three months old at time of immunization showed detectable antitoxin within two weeks. By Fisher's exact method (from Mainland's tables[12]) this difference in the incidence of measurable antitoxin two weeks after immunization between the infants under two months old and those six months old is significant at the 5% level.

One month after immunization 9 of 10 infants six months old had responded with antitoxin levels over .002 U./cc. But only one of 11 infants under 2 weeks of age at immunization showed antitoxin in one month. Of the 10 one month old infants immunized, seven had responded within a month. Mainland's tables (Fisher's Exact Method[12]) applied to this data shows that the differences in incidence of response one month after immunization between the infants under two weeks old and the older two age-groups of infants are significant at the 5% level.

A more detailed analysis of data is presented in table 1, in which are found for each age-group the number of cases in each time period after immunization, the mean antitoxin response and the standard error of the mean.

Because the first two columns in table 1 (two weeks after immunization and one month after immunization) contain data including infants whose titers were under .002 U./cc. it is not possible to calculate the true mean antitoxin responses for these different groups.

Since the present investigators did not titrate below .002 U./cc., any specimen measured as less than .002 U./cc. might represent any level from below this figure to zero. So for purposes of presentation in these columns the mean has been calculated in two ways. The first figure given represents the mean calculated as if each value under .002 U./cc. equals zero. The second figure given is the mean calculated as if less than .002 U./cc. equals .001 U./cc. It is reasonable to assume that the true mean lies between these limits. But because the exact true mean is not actually known, this data in the first two columns is not subject to analysis by such procedures as the t-test or analysis of variance. This difficulty does not apply to the remaining columns, beginning two months after immunization when true means can be calculated.

Two months after immunization, the differences between age-groups were shown by analysis of variance to be significant at the 5% point. Three to four months after immunization the differences are not significant because the number of cases is too small. Six months after immunization, however, the following differences are significant at the 5% level: between infants under 2 weeks of age and those one month old at immunization, and between infants one month old and all those over two months old (including six months).

Response to Tetanus

From the above data, it is clear that there is a strong age-differential in the response of infants to a potent diphtheria toxoid on alum. In order to obtain data for another antigen-antibody system, the authors injected a smaller number of infants with a single dose of 163 Lf tetanus toxoid on alum. This dosage of tetanus toxoid contained an amount of antigenic protein nitrogen roughly equivalent to that contained in the 100 Lf diphtheria toxoid dose, and was injected in the same volume of 0.5 cc. in order to permit direct comparison of the antibody responses to these two antigens.

In all, 27 infants who had no detectable circulating tetanus antitoxin, and who ranged in age from under 2 weeks of age to 6 months of age were immunized, each with a single dose of tetanus toxoid. These infants also received an injection of diphtheria toxoid at the same time but in the opposite arm and were included in the foregoing study on diphtheria. The results up to six months after the injection are shown in table 2 and graphed in chart 2.

As was the case after diphtheria immunization, it appears clear that younger infants did not respond as well as older infants. However, there are some important differences between the responses to diphtheria and to tetanus. In the first place, no infant one month

old or younger had produced detectable diphtheria antitoxin two weeks after immunization, while during the same time period, 9 out of 19 infants had developed .01 u./cc. tetanus antitoxin or more.

Secondly, the difference between the responses of infants 2 weeks of age and those one month old is not nearly as large for tetanus as it is for diphtheria.

It should be noted, however, that in all time periods except the first (two weeks after immunization), the youngest infants show the poorest response. The apparent variation in the first time period (two weeks after immunization), when the mean for two week

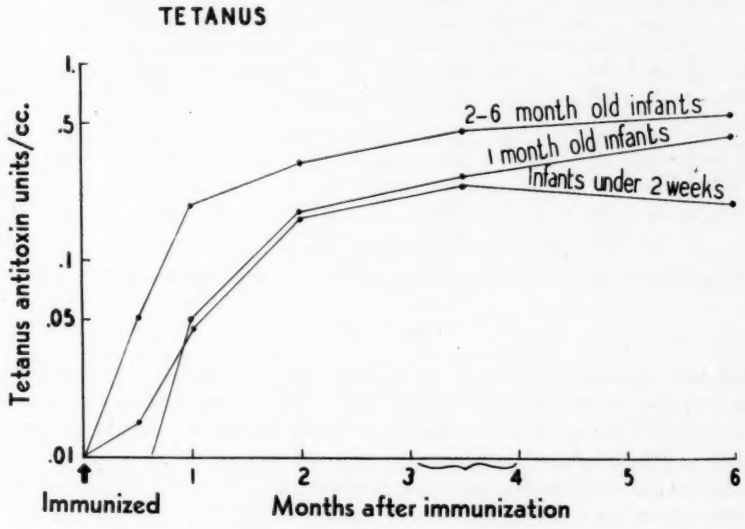

CHART 2. Tetanus immunization: Mean response of infants of different age groups. Antitoxin titer is graphed on logarithmic scale.

old infants is higher than that for one month old infants, is caused by the very high titer of a single case and might not be valid if larger numbers of cases had been available.

STATISTICAL EVALUATION

Because of the small numbers of cases, not all the differences between age-groups shown in chart 2 are significant at the 5% level. It is not possible to demonstrate a significant difference between the antitoxin responses of infants under 2 weeks of age when immunized, and those of infants one month old.

However, if these two groups are combined so that comparison is made between the responses of all infants one month old or younger when immunized, and the responses of infants 2 to 6 months old, some differences can be demonstrated. By the t-test, the differences between these two groups can be shown to be significant at the 5% level for the following time periods: two weeks after immunization, one month after immunization, and two months after immunization. Analysis of variance of the data on infants followed six months after immunization showed that the number of cases was too small for statistical significance.

TABLE 2

ANTITOXIN RESPONSE IN UNITS OF TETANUS ANTITOXIN/CC. SERUM OF INFANTS OF DIFFERENT AGES TO SINGLE IMMUNIZATION WITH 163 LF TETANUS TOXOID (ALUM PPT.). ANTITOXIN RESPONSE IS GIVEN AS MEAN LEVEL ± STANDARD ERROR OF MEAN.

Age at Time of Immunization	Time After Immunization									
	2 Wk.		1 Mo.		2 Mo.		3–4 Mo.		6 Mo.	
	No. of Cases	Antitoxin* Level	No. of Cases	Antitoxin* Level	No. of Cases	Antitoxin Level	No. of Cases	Antitoxin Level	No. of Cases	Antitoxin Level
2 wk.	10	.015± .010	9	.044± .015	7	.164± .032	7	.243± .054	0	.198± .052
1 mo.	9	.007± .003	8	.049± .013	6	.170± .038	4	.262± .052	2	.425
2–6 mo.	8	.05± .011	7	.189± .044	7	.310± .052	3	.45	2	.55

* In these columns, values of less than .01 units were treated as if equal to zero.

DISCUSSION

The infant obviously improves in his ability to form diphtheria and tetanus antitoxin during early life. In the case of diphtheria, there is little if any difference between antibody formation at the age of 2 to 4 months and that at the age of 6 months. This appears to be true of tetanus antitoxin production as well, although we have less data for tetanus. From this we can conclude that the major development in the ability to form diphtheria and tetanus takes place during the first few months of life. It is quite possible that the individual has approached physiologic maturity in this regard by about the third to sixth month. However, this could only be verified by studying the response of much older individuals who have not been previously immunized.

In response to both the antigens, infants were able to produce a level usually considered protective of antitoxin at all age levels. It is true that far more potent antigens were used than those used clinically; however, in the conventional immunization schedules a series of 2 or 3 injections at monthly intervals are given instead of the single injection that the authors used. The maturation of the individual during the series plus the booster effect of the repeated injections appears to be adequate to make up for the difference in potency of the antigen.[3] It is conceivable that with a weak antigen which is just capable of producing protection under optimal conditions, the age at which the injections are given may be a decisive factor.

It should be pointed out that in this study the authors have used antigens precipitated on alum in order to increase the antigenic effect. Since alum releases the antigen over a period of weeks, it was not possible to accurately measure the antibody performance during the first two weeks of life. It is quite possible that this is poorer than the curves for the two week old group would indicate.

It is tempting to compare the antibody curves derived from diphtheria immunization with those of tetanus. It can be readily seen that the tetanus curves rise earlier, and reach

higher levels than the diphtheria curves. The peak of both curves is reached about three months after immunization and then a gradual decline begins.

However, such a comparison must be interpreted with caution. The antigens used are not pure diphtheria or tetanus antigens. In addition to unknown contaminants which may significantly alter the antibody production, the presence of alum may affect the two systems differently. The authors are not comparing the ability of the individual to produce diphtheria or tetanus antitoxin, but only his ability to respond to the particular antigens used. It must be also borne in mind that the antibodies to be compared are measured by two different animal technics. Since both are toxin-antitoxin neutralization technics using the animal merely as an end-point, such a comparison seems valid.

With these reservations in mind, it may be said that the tetanus preparation was the more effective antigen. This appears to be true of preparations used clinically as well.

In the diphtheria curves for the younger age groups, there is a lag of one month after immunization before demonstrable antibody appears. The tetanus antibody curves rise much earlier after immunization. This suggests that diphtheria antibodies may also be formed early but at a level below that which was detectable by the technic used. This would produce the apparent lag in response. It would be interesting to see if a much weaker tetanus antigen than the one used would produce a similar lag effect.

Making generalizations from data obtained in a restricted sphere must be done with caution. The following conclusions seem reasonable:

1. The infant is capable of antibody formation from birth.
2. The ability to form antibodies improves during early life. In the case of diphtheria antitoxin, the major development appears to take place during the first two months of life. This is probably true of tetanus, too, but may or may not be true of other antigen-antibody systems.
3. In deciding the advisability of immunization early in infancy, consideration must be given to the potency of the antigen to be used.

Summary

Forty infants from 1 week to 6 months of age who had no circulating antitoxin were immunized with one injection of a high titer diphtheria toxoid on alum and their antitoxin responses were followed at regular intervals up to six months afterwards.

The ability to form antitoxin improved significantly during the first two months of life. No significant difference could be demonstrated between the response of infants 2 to 4 months of age and that of infants 6 months of age. (In the statistical tests, the 5% level was adopted as indicating significance.)

Twenty-seven of these infants were immunized at the same time in the opposite arm with a single dose of tetanus toxoid on alum. The response to tetanus immunization was faster and better in infants from 2 to 6 months of age than in infants 1 month of age and younger. The response to the tetanus toxoid preparation was faster and better than the response to the diphtheria toxoid preparation.

The following conclusions are drawn: A. The infant can form antibodies from birth. B. The ability to form antibodies improves during early life. For diphtheria and tetanus antitoxin, the improvement is rapid during the first two months and then is much slower. C. The advisability of early immunization is related to the potency of the antigen to be used.

ACKNOWLEDGMENT

The authors are indebted to Dr. Donald Mainland, Professor of Medical Statistics, New York University College of Medicine, for his extensive help in the statistical evaluation of this data. Dr. A. J. Vignec and the staff of the New York Foundling Hospital aided in making available the facilities for this study.

REFERENCES

1. Baumgartner, Leona, Relationship of age to immunological reactions, Yale J. Biol. & Med. **6**:403, 1934.
2. McKhann, C. F., and Kapnik, I., Immunity and susceptibility to disease in early infancy, J. Pediat. **13**:907, 1938.
3. Peterson, J. C., and Christie, A., Immunization in young infant, Am. J. Dis. Child. **81**:483, 1951.
4. Vahlquist, B., Studies on diphtheria: Decrease of natural antitoxic immunity against diphtheria, Acta paediat. **35**:117, 1948.
5. Vahlquist, B., and Hackzell, G., Studies on diphtheria: Duration of immunity against diphtheria following vaccination as compared with that following clinical disease and carrier state, Acta paediat. **35**:149, 1948.
6. Di Sant'Agnese, P., Combined immunization against diphtheria, tetanus and pertussis in newborn infants. I. Production of antibodies in early infancy, PEDIATRICS **3**:20, 1949.
7. Di Sant'Agnese, P., Combined immunization against diphtheria, tetanus and pertussis in newborn infants. II. Duration of antibody levels; Antibody titers after booster dose; Effect of passive immunity to diphtheria on active immunization with diphtheria toxoid, PEDIATRICS **3**:181, 1949.
8. Sako, W., Studies on pertussis immunization, J. Pediat. **30**:29, 1947.
9. Cooke, J. V., Antibody formation in early infancy against diphtheria and tetanus toxoids, J. Pediat. **33**:141, 1948.
10. Schmidt, S., Purification et concentration de la toxine-antitoxine diphthériques, Ann. inst. Pasteur **46**:202, 1931.
11. Fraser, D. T., presented by Fitzgerald, J. G., Technique of method for quantitative determination of diphtheria antitoxin by skin test in rabbits, Tr. Roy. Soc. Canada **25**:175, 1931.
12. Mainland, D., Statistical methods in medical research. I. Qualitative statistics (enumeration data), Canad. J. Research **26**:1, 1948.

SPANISH ABSTRACT

Estudios de Inmunología en el Niño Recien Nacido
I. Edad y Producción de Anticuerpos

Se estudió la correlación entre la edad y la capacidad para producir anticuerpos en cuarenta niños cuya edad varió desde una semana hasta seis meses y que no tenían antitoxinas diftérica o tetánica en su sangre. Después de administrarles una inyección única de 100 l.f. (unidades serológicas de floculación) de toxoide diftérico en alumbre y a veintisiete de ellos 163 l.f. de toxoide tetánico en alumbre, se midió su respuesta de anticuerpos periódicamente hasta seis meses después de la fecha de su inmunización.

Todos los lactantes respondieron con la formación de antitoxina, respuesta que mejoró progresivamente de acuerdo con la edad del niño, siendo a los 2 meses de edad cuando se estabilizó dicha respuesta. Efectivamente, los niños inmunizados cuando tenían seis meses no respondieron mejor, en forma significativa, que el grupo de los 2 - 4 meses.

Aunque la respuesta en los niños más pequeños no fué tan buena como en los mas grandes, aún en aquéllos se alvanzaron niveles de antitoxina generalmente considerados como protectores.

477 First Avenue

CONVULSIONS AND DEAFNESS FOLLOWING INGESTION OF DDT

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IN VIEW of widespread use of DDT as an insecticide, one may well anticipate an increased incidence of poisoning due to this compound. Previous authors have emphasized toxic central nervous system manifestations[1-3] and hematologic phenomena[4] consequent to its excessive absorption. It is the authors' purpose to report a case of DDT poisoning which resulted in convulsions and transitory deafness.

CASE REPORT

History: J. W., a previously well 2 yr. old Negro male, was admitted to the Children's Hospital because of generalized convulsions. Two hours prior to admission the patient had drunk an unknown quantity of fly spray which contained DDT as the essential ingredient. The concentration of DDT was 5% but the solvent was unknown. Approximately 1 hr. after ingestion the child became unconscious and had a generalized, sustained convulsion. There had been no previous seizures and no history of convulsions among other family members.

Admission Physical Examination: The child was markedly lethargic, had a distended abdomen, and was having generalized convulsions. The lungs were clear and tachycardia present. There was no evidence of nuchal rigidity. No signs of bleeding of skin or mucus membranes were observed.

Laboratory: Routine blood and urine examinations revealed no abnormalities. Because of the strong opinion that the convulsions were due to central nervous system stimulation by DDT, the cerebrospinal fluid was not examined until the seventh hospital day at which time it was normal.

Treatment and Hospital Course: During the 1st 5 hr. following admission, 13 grains of barbiturates were administered intravenously or intramuscularly and 2 grains of chloral hydrate were given rectally before the convulsions ceased. The patient also received oxygen and a slow, continuous intravenous drip of 10% glucose in distilled water.

Seven hours after admission the patient became apneic. This was presumably a barbiturate effect. Artificial respiration was instituted and 0.5 cc. coramine® was injected intramuscularly. Subsequent to these measures respiratory difficulty was alleviated. During the remainder of the first hospital day, the patient's condition continued to be critical. A transfusion of 200 cc. whole blood was given, followed by 500 cc. 5% glucose in distilled water as a continuous intravenous drip. The blood pressure remained in the range of 70 to 90 mm.Hg systolic and 30 to 40 mm.Hg diastolic.

On the second hospital day the temperature rose to 39.7°C. without demonstrable cause. However, penicillin and chloramphenicol were administered. Lethargy persisted and parenteral fluid therapy was required for 48 hr. after admission. The temperature gradually returned to normal after 3 days and remained so throughout the hospital stay.

Four days after admission 2 generalized seizures occurred which were of such short duration that they ceased before sedation could be instituted. One of these convulsions was precipitated by an attempt to take the temperature rectally. The next day another seizure occurred, also of short duration, and at this time one-half grain of phenobarbital was administered orally and repeated 4 times a day with no further convulsive episodes.

Improvement was slow and lethargy and ataxia continued to dominate the clinical picture. On the twelfth day it was determined that loud noises elicited no reaction and that the patient was deaf. A caloric test performed bilaterally did not cause nystagmus.

The patient was discharged after 17 days in the hospital and all medication was discontinued at this time. He was seen in the outpatient clinic 5 days later. Several convulsive seizures had occurred

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during the previous 24 hr. for which phenobarbital therapy was re-instituted. Hearing continued to be severely impaired.

When seen 2 mo. later he had experienced no further convulsions although sedation had been discontinued by the parents. Hearing was normal and it was stated that this had begun to improve approximately 1 wk. after the first clinic visit. The patient's mental and neurologic status was apparently normal for his age.

Discussion

The synthetization of DDT was first effected by Zeidler in 1874, but only in recent years has its use as an insecticide become widespread. DDT in the powdered form causes no local or systemic toxic effects when applied to either the broken or unbroken skin. However, when dissolved in certain oils and solvents deleterious effects of DDT may become evident. Animal experimentation has demonstrated not only its severe toxicity but also has suggested a wide variation in the dose necessary to produce injury.[5,6] Therefore, one should be alert to potential perils of absorption of a seemingly small amount.

In animals, manifestations of DDT intoxication, as reported by Neal and Von Oettingen,[7] are confined largely to symptoms referable to the central nervous system. These include anorexia, generalized tremors, nervousness, hyperexcitability, impaired coordination, clonic-tonic type of convulsions, and coma, ending in death. Similar effects in humans have been observed by other investigators.[1,2] In addition, Karpinski[4] has recorded the occurrence of purpura in five children with DDT poisoning. Three of his cases exhibited signs of nervous system involvement. These included irritability, nervousness and impaired coordination. One patient had clonic-tonic convulsions. Although central nervous system symptoms dominate the clinical picture of poisoning in both animals and humans, surprisingly few pathologic changes in neural tissue have been demonstrated in autopsy material. The principal pathologic lesions have been present in hepatic and pulmonary tissues.[1,8,9]

The case presented herein is considered to be unusual because of the transitory loss of hearing and the severity and long duration of the convulsive seizures. The latter coincides with the recognized slow excretion of DDT. In view of the paucity of reported autopsies in patients dying of DDT poisoning, the pathogenesis of the transient deafness cannot be explained. Persistence of convulsions despite heavy sedation indicates that marked stimulation of the central nervous system occurred. It is interesting to note that mechanical stimulation produced a seizure in this patient, a phenomenon which has been described in animals[7] and likened to convulsive episodes seen in strychnine poisoning.

Although the solvent for the DDT in this case is not known, the authors' opinion is that the toxic signs and symptoms are due to DDT per se. This opinion is based on the fact that the usual solvent for DDT is a hydrocarbon, poisoning from which results in central nervous system depression characterized by drowsiness and symptoms of inebriation similar to those from alcohol.[10]

Conclusions

A case of DDT poisoning in a two year old child is presented. Transitory deafness and severe convulsive seizures dominated the clinical picture, but uneventful recovery ensued.

Effects of DDT intoxication on the nervous system are discussed.

References

1. Hill, K. R., and Robinson, G., Fatal case of DDT poisoning in child, Brit. M. J. **2**:845, 1945.
2. Hill, W. R., and Damiani, C. R., Death following exposure to DDT, New England J. Med. **235**:897, 1946.

3. Wigglesworth, V. B., Case of DDT poisoning in man, Brit. M. J. 1:517, 1945.
4. Karpinski, F. E., Purpura following exposure to DDT, PEDIATRICS **37**:373, 1950.
5. Draize, J. H., Nelson, A. A., and Calvery, H. O., Percutaneous absorption of DDT in laboratory animals, J. Pharmacol. & Exper. Therap. **32**:159, 1944.
6. Woodard, G., Nelson, A. A., and Calvery, H. O., Acute and subacute toxicity of DDT in laboratory animals, J. Pharmacol. & Exper. Therap. **82**:152, 1944.
7. Neal, P. A., and Von Oettingen, W. F., Toxicity and potential dangers of DDT to humans and warm-blooded animals, M. Ann. District of Columbia **15**:15, 1946.
8. Lillie, R. D., and Smith, M. I., Pathology of experimental poisoning in cats, rabbits and rats with 2,2 bis-parachlorphenyl-1,1,1 trichlorethane, Pub. Health Rep. **59**:979, 1944.
9. Reports to the Council on Pharmacy and Chemistry: Pharmocologic and Toxicologic Aspects of DDT (Chlorophenothane U.S.P.), J.A.M.A. **145**:728, 1951.
10. Mitchell-Nelson Textbook of Pediatrics, edited by W. E. Nelson, Philadelphia, W. B. Saunders Company, 1950, p. 750.

SPANISH ABSTRACT

Convulsiones y Sordera Después de la Ingestión de DDT

En vista del uso extenso de DDT como insecticida se debe anticipar un aumento futuro en la incidencia de envenenamientos por esta substancia. Después de su absorción excesiva se han hecho notar manifestaciones tóxicas sobre el sistema nervioso central y trastornos hematológicos. En este artículo se reporta un caso de envenenamiento con DDT que produjo convulsiones y sordera transitoria.

Se trató de un niño negro de 2 años de edad hospitalizado con un cuadro de convulsiones generalizadas. Dos horas antes de su admisión había bebido una cantidad no determinada de cierto insecticida que contenía como ingrediente esencial DDT a la concentración de 5%, en un solvente desconocido. Las convulsiones se iniciaron una hora después de la ingestión del líquido.

Al examen físico de admisión se le encontró letárgico, con meteorismo y convulsiones generalizadas. Los exámenes de laboratorio de rutina no mostraron datos anormales. El líquido cefaloraquídeo examinado al séptimo día fué normal.

Se le administraron barbitúricos por vía parenteral; hidrato do cloral por vía rectal; oxígeno y venoclisis lenta contínua de solución de glucosa al 10% en agua destilada.

Siete horas después de ser admitido presentó apnea atribuible probablemente a los sedantes, cediendo con respiración artificial e inyección intramuscular de 0.5 c.c. de coramina. Durante las primeras 24 hs. su estado fué crítico, se le aplicó una transfusión de 200 c.c. de sangre total, seguida de venoclisis de 500 c.c. de solución glucosada al 5%. El segundo día la temperatura se elevó a 39.5 centígrados sin causa demostrable, retornando a lo normal al tercer día y permaneciendo en dichas condiciones por el resto del período de hospitalización. Se le administró penicilina y cloranfenicol, requiriéndose además líquidos parenterales en las siguientes 48 horas a su admisión. Al cuarto día presentó 2 convulsiones generalizadas, de duración corta, y hubo otra más al quinto día. La mejoría fué lenta y en el cuadro clínico continuaron predominando la ataxia y la letargia. Al doceavo día se comprobó que el paciente se encontraba sordo. Fué dado de alta después de 17 días de estar internado, siendo nuevamente examinado en la consulta externa 5 días mas tarde, por haber presentado convulsiones, reinstituyéndose la terapeútica con fenobarbital. Se apreció que persistía la sordera. Dos meses mas tarde fué estudiado sin que se encontrara dificultad auditiva y sin que los padres reportaran que hubieran habido mas convulsiones.

El caso presentado se considera que es raro debido a la pérdida transitoria de la audición y a la severidad y larga duración de las convulsiones. En vista de las pocas autopsias reportadas en enfermos muertos por envenenamiento con DDT es difícil de explicar la patogénesis de la sordera. La presencia de convulsiones, a pesar de la terapeútica sedante enérgica, hacen pensar que hubo un estímulo acentuado del sistema nervioso central. Aunque el solvente para el DDT, en este caso no es conocido, la opinión de los autores es de que los signos tóxicos y los síntomas fueron debidos al DDT por sí mismo.

20 South Dunlap

PHAGOCYTIC AND AMEBOID ACTIVITIES OF THE LEUKOCYTES IN THE NEWBORN INFANT

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THE low resistance to infection characteristic of the newborn infant is due to a large extent to a poorly developed humoral defense mechanism resulting from the young infant's inexperience with infection. That imperfectly functioning leukocytes may be an additional contributing factor to this poor resistance is suggested by certain peculiarities in behavior of the white blood cells during the neonatal period.

The variability of the white cell count in the newborn period is an observation well known to clinicians dealing with this age group. Unusually high white counts, which in older age groups would be taken to indicate the presence of infection, are often found in the newborn infant without any other evidence of disease, whereas infections which usually produce a high leukocytosis in older children and adults do not always do so in the newborn. Wide variations and fluctuations in the number of white cells, particularly of the polymorphonuclear neutrophils,[1] may have no apparent relationship to health or disease.

These and similar observations have suggested the desirability of an experimental study of some of the functions of newborn leukocytes. In the present paper a comparative study of phagocytic ability and ameboid activity of newborn white blood cells is reported.

In spite of the large volume of work on phagocytosis in the literature, few references to the phagocytic ability of newborn leukocytes could be found. Of the earlier work, Tunicliffe[2] in 1910 studied the phagocytic activity of leukocytes in infancy towards streptococci, pneumococci and staphylococci and found that the leukocytes at birth were "a little less" active than adult leukocytes, their activity diminished considerably during the first months of life and did not reach that of adult leukocytes until about the third year. More recently, Bracco[3] found the phagocytic potency of fetal placental whole blood towards staphylococci to be lower than that of maternal blood.

METHODS

The phagocytic activities of 32 normal full-term newborn babies, including one pair of identical twins, were compared to those of 27 mothers and 6 normal nonpregnant adults. Similarly, observations on the ameboid motility of the leukocytes of 33 infants were made. Newborn leukocytes were obtained from cord blood. Maternal blood was obtained during delivery. With 2 exceptions, the deliveries were done under ether anesthesia.

Twenty milliliters of fetal placental blood were allowed to run from the umbilical vein, immediately after the placenta had separated, into a large tube containing a solution of equal parts of the disodium and trisodium salts of ethylene-diamine-tetraceti: acid (sequestrin®)† to a final concen-

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† Although this anticoagulant inhibited phagocytosis, the inhibition was reversible by subsequent washing and resuspension in an EDTA-free medium.

tration of 0.35%. The same quantity of adult blood was obtained by venipuncture with a siliconed syringe and collected in similar fashion. All subsequent treatment of both newborn and adult blood was simultaneous and identical. The red cells were separated by differential sedimentation with dextran,[4] leaving the white cells in suspension in the supernatant plasma, which was drawn off and centrifuged in D'hont tubes* at 120 g (800 to 1,000 rpm for an average sized laboratory centrifuge) for 1 min., resulting in complete recovery of the leukocytes at the bottom of the lower tube. The clear, cell-free plasma in the upper tube was then poured off and the cells washed 3 times in modified Hanks solution adjusted to pH 7.4 by repeated filling of the upper tube and centrifugation. The end result was a suspension of 1 to 2 cc., containing 40 to 100 thousand leukocytes/cmm. All glass surfaces to which the cells were exposed were siliconed.

Starch granules were used as test particles[5] and normal human serum, which is essential to starch phagocytosis[5] was added to the phagocytic mixtures. As sera appeared to vary considerably in their opsonizing effect, frozen pooled cord serum was used throughout the greatest part of the study to achieve standardization. Sera were diluted in modified Hanks solution.

Phagocytic mixtures were prepared in small test tubes, each mixture consisting of equal parts of (1) infant or adult washed cell suspension, (2) starch suspension and (3) serum dilutions. The tubes were shaken vigorously to allow thorough mixing. One drop each of a mixture containing infant cells and of a corresponding mixture containing adult cells was placed on each end of a slide, covered with a cover slip and the edges sealed with paraffin. The slides were incubated at 37° for 20 min. and examined under phase microscopy.

Only polymorphonuclear neutrophils were counted, usually 100 cells. The cells were classified as to their ameboid activity, and to the number of starch particles ingested by each cell. Differences in ameboid activity between infant and adult cells were found to be most marked in pure Hanks solution without added serum. Counts for ameboid activity were therefore carried out in this medium. The percentages of phagocytic cells, i.e., cells containing one or more starch granules, as well as phagocytic indices were calculated. The latter express the average number of particles ingested/cell and in this study represent approximate values only, as it was extremely difficult to count with accuracy more than 5 particles/cell. All cells containing 5 or more particles were therefore classified as 5+ even though many so classified actually contained well over 10 particles.

Results

A. Phagocytic Activity: The phagocytic activity of newborn leukocytes was found to be, under certain experimental conditions, considerably lower than that of adult cells.

By varying the amount of normal human serum added to the phagocytic mixtures, the rate of phagocytosis could be varied at will. The phagocytosis-promoting power of individual sera varied considerably. However, with a given serum it was possible, by setting up a series of progressive dilutions, to obtain a whole spectrum of phagocytic activities, ranging from full phagocytosis, with all cells packed with starch granules and hardly any free particles left outside the cells, down to complete absence of any phagocytic activity. No appreciable difference between the phagocytic activities of newborn and adult leukocytes could be found at both extremes of this scale. Near the upper end, where phagocytosis proceeded under optimal conditions, infant as well as adult cells showed full activity, whereas towards the lower end the percentages of phagocytic cells and the phagocytic indices were too small to allow any statistically valid conclusions. Within a certain range about the middle of the scale, however, differences in phagocytic activity of newborn and adult cells could be clearly demonstrated (chart 1). Results obtained with serum dilutions falling within this range are graphically presented in charts 2 and 3. Earlier in the study the opsonizing effect of each serum used could not be predicted and 3 to 4 observations with serial serum dilutions, as in chart 1, had to be made

* "The centrifugal syphon" devised by Dr. M. D'hont, to be published. Obtainable from Macalaster Bicknell Co., Cambridge, Mass.

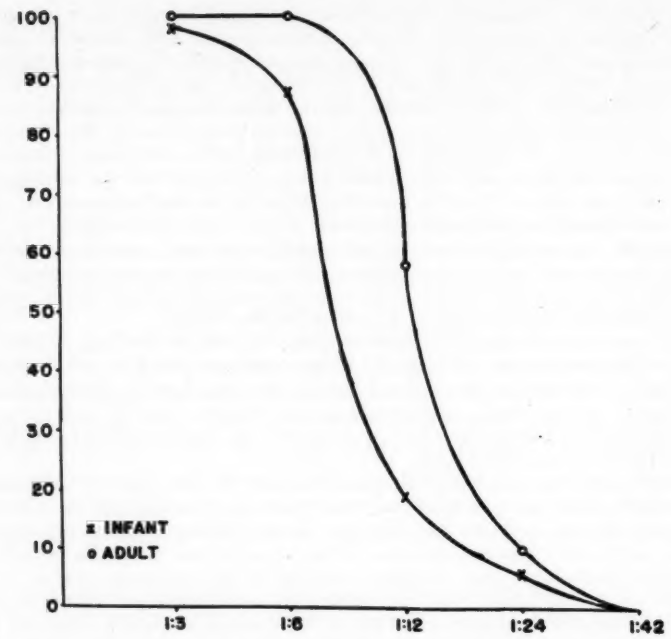

CHART 1. Phagocytosis by infant and adult leukocytes in presence of progressive serum dilutions. Abscissae: concentration of serum in phagocytic mixture. Ordinates: percentages of phagocytic cells.

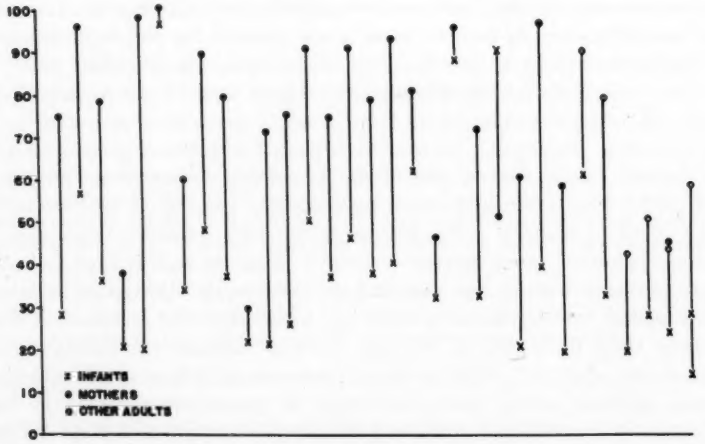

CHART 2. Phagocytic activity of infant and adult leukocytes expressed as per cent of phagocytic cells. Difference between each infant and its adult control is represented by solid line. Last 2 observations, respectively, represent simultaneous comparison of infant leukocytes to those of mother and another adult, and pair of identical twins.

with each set of cells to bring out the difference between newborn and adult cells. In these instances the observation showing the maximum difference in either direction is recorded. With the use, later in the study, of a standardized frozen pooled cord serum, it became possible to obtain results falling within the "effective" range with a single observation, using one dilution (1:6) of the standard serum for each set of cells. These results do not necessarily show the maximum difference in phagocytic activity within each pair of newborn and adult leukocytes.

In chart 2 the phagocytic activities of infant and adult leukocytes are shown as percentages of phagocytic cells, i.e., the number of cells which have ingested one or more particles, expressed as a percentage of the total number of cells counted. The percentage of phagocytic cells found for each infant and that of its corresponding adult control are plotted on each end of a vertical line, which represents the difference between them. It will be seen that the infant cells show a lower phagocytic activity in all but one of the 32 observations. The difference between the phagocytic activity of infant cells and that of the corresponding adult control exceeded 30% in 20 observations, while in 16 observations the difference was 40% or over.

In chart 3 the phagocytic activity of each infant is expressed as a fraction, or percentage, of its corresponding adult control. It will be noted that of the 32 observations recorded, in 23 the phagocytic activities of infant leukocytes were 55% or less of their corresponding adult controls. Twenty-one observations are grouped in the 30 to 55% range.

The scattering of results for both infants and adults in chart 2 deserves some explanation. Uncontrollable variables, such as the amount of damage sustained by the cells and the length of time from the moment the blood was collected until the cells were ready for microscopy, slight variations in pH and traces of impurity on the glass surfaces of slide and cover slip might be partly responsible for this variation. The potency and concentration of the serum used, which determined the place of any particular measurement on the dilution curve (chart 1), was also of some importance. However, the scattering of results observed even when the same concentration of a standardized frozen pooled serum was used (first 19 observations in chart 2) would indicate that the phagocytic power of the leukocytes themselves is subject to variation in different individuals.

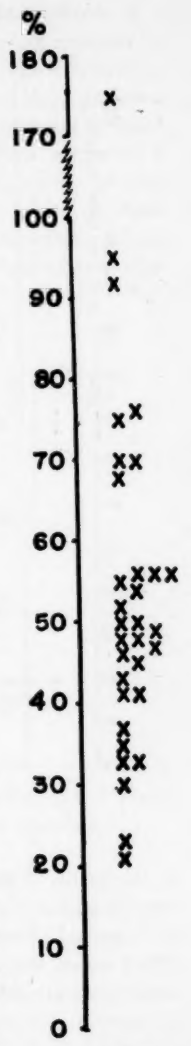

CHART 3. Phagocytic activities of infant leukocytes as percentages of their corresponding adult controls.

With these limitations in mind, it was not anticipated that all measurements from either adult or neonatal leukocytes would fall within any particular range specific for that age and conclusions were based solely on the comparison of phagocytosis by the individual infant's cells with that by the cells of the corresponding adult control. No attempt is made to correlate individual observations to each other or to calculate mean values for the whole series. The general trend is evident from charts 2 and 3 and its statistical significance is obvious.

B. Ameboid Movement: There was a striking difference between the ameboid motility of newborn and adult leukocytes suspended in Hanks solution. In chart 4 each end of a vertical line represents the ameboid activity of the leukocytes of an infant and its corresponding adult control as percentages of ameboid cells, i.e., the number of cells showing ameboid movement expressed as a percentage of the total number of cells counted. Chart 5 shows the ameboid activities of infants' leukocytes expressed as fractions, or percentages, of their corresponding adult controls. The number of infant leukocytes showing ameboid activity was consistently lower than that of adult cells under the same experimental conditions. Numbers of ameboid cells, however, give an incomplete picture of the inferiority in ameboid activity of newborn leukocytes as, in addition, a marked difference

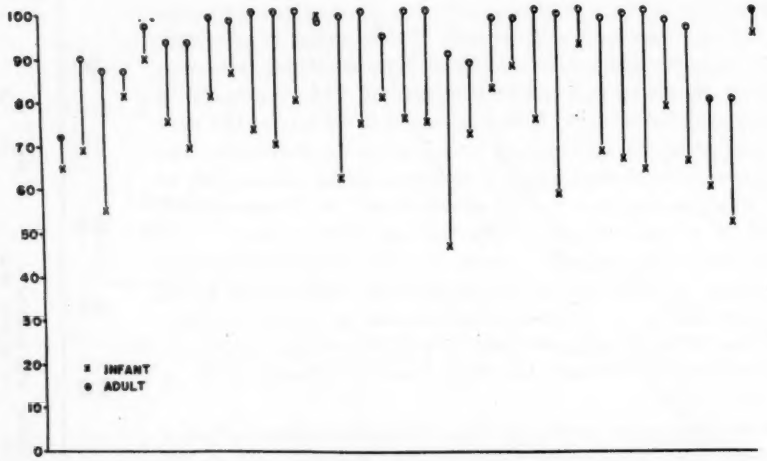

CHART 4. Ameboid activity of infant and adult leukocytes expressed as per cent of ameboid cells. Difference between each infant and its adult control is represented by solid line.

in the quality of the ameboid motility was observed. Whereas the majority of adult cells were elongated, with long pseudopods and displayed a lively activity, infant cells classified as "ameboid" were often sluggish, almost round, with short and plump pseudopods. When serum was added to the suspensions, the differences disappeared and the infant leukocytes were indistinguishable from adult cells.

DISCUSSION

A study of phagocytosis would not be complete without consideration of humoral factors. In the present study, which is primarily concerned with the inherent phagocytic ability of the leukocytes, the serum factor was disregarded and newborn leukocytes were compared to adult cells in the presence of the same serum in both phagocytic systems. However, in the few instances in which the phagocytosis-promoting power of newborn and adult serum was compared, the serum from the newborn was consistently less potent. The number of observations so far is small and this aspect of the problem will be taken up in a later study.

Maternal leukocytes were used as controls throughout the greater part of the study, as it was thought that the hormonal status of the infant at birth was better reflected in

its mother's blood than in the blood of normal, nonpregnant adults. Any possible difference in phagocytic activity due to the effect of estrogens would thus be minimized. The same may apply to a certain extent to the possible part played by adrenal cortical steroids, both mother and child being subject to the stress of childbirth and presumably the increased production of adrenal cortical steroids associated with it. That hormonal influences did not materially affect the results is suggested by the observation that phagocytic activities of mothers at term and those of normal nonpregnant adults used as controls all fell within the same range, and the activity of infant cells was lower when compared to both groups.

The leukocytes obtained from newborn blood had been exposed to whatever varying degrees of anoxia occur in the fetus and infant before and during delivery. There is no evidence that this anoxia *in vivo* had irreversibly modified their phagocytic ability *in vitro*. Outside the body, the washed leukocytes of infants and adults had similar access to oxygen by diffusion through the suspending medium. Under these semi-anaerobic conditions, with ample glucose supplied in the medium, infant cells, with their higher efficiency in utilizing an anaerobic metabolism,[6] would be expected to perform better than adult cells.

The qualitative and quantitative differences observed in ameboid motility of newborn and adult leukocytes do not account for the lower phagocytic activity of the former. The present study has confirmed previous observations[7] that ameboid activity does not run parallel to phagocytosis and is increased by serum. The decreased ameboid activity of infant cells was observed in pure salt solution, in which medium both infant and adult cells showed hardly any phagocytic activity, whereas the lower phagocytic activity of neonatal leukocytes was demonstrated in media containing serum, in which infant and adult cells were indistinguishable as to their ameboid motility.

In conclusion, the present findings would indicate an inherent functional difference between newborn and adult leukocytes, in line with similar differences and functional immaturity found in other organs and systems by various workers.[8–10]

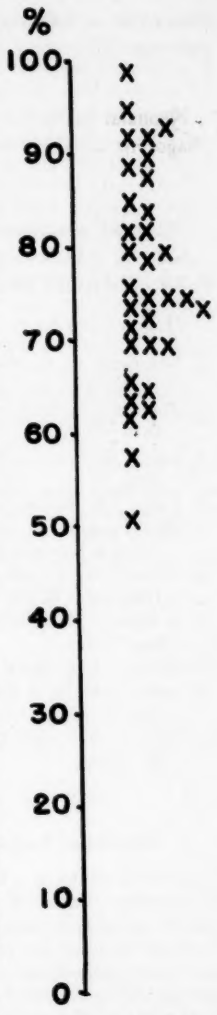

CHART 5. Ameboid activities of infant leukocytes as percentages of their corresponding adult controls.

The data here reported were obtained under artificially created suboptimal conditions not likely to be reproduced *in vivo*. Nevertheless they represent objective evidence of an inferior performance by neonatal leukocytes, the significance of which in the newborn infant's notoriously poor resistance to infection is difficult to evaluate. Pending further study, this report would serve to draw attention to the existence of a biologic difference between newborn and adult leukocytes.

Metabolic studies on neonatal leukocytes are now in progress. It is also planned, when methods requiring a smaller amount of blood are available, to follow the ameboid and

phagocytic activities of leukocytes through the first days and weeks of life and in prematurity.

Summary

Neonatal leukocytes obtained from cord blood were found to have lower ameboid and phagocytic activities when compared to maternal leukocytes and those of other adults.

Acknowledgment

This work was carried out under the direction of Dr. Clement A. Smith.

Grateful acknowledgment is also made of the assistance and advice of Dr. James L. Tullis of Harvard Medical School and for the use of certain facilities in his laboratory.

References

1. Washburn, A. H., Blood cells in healthy young infants. III. Study of 608 differential leukocyte counts, with final report on 908 leukocyte counts, Am. J. Dis. Child. **50**:413, 1935.
2. Tunicliffe, R., Observations on anti-infectious power of blood of infants, J. Infect. Dis. **7**:698, 1910.
3. Bracco, G., Potere fagocitario del sangue placentare fetale, Gior. di batteriol. e immunol. **38**:449, 1948.
4. Tullis, J. L., Personal communication to the author.
5. Hamburger, H. J., in Handbuch der biol. Arbeitsmethoden, edited by E. Abderhalden, Berlin, Urban & Schwarzenberg, 1927, vol. 4, pt. 4, p. 977.
6. Himwich, H. E., and others, Mechanism for maintenance of life in newborn during anoxia, Am. J. Physiol. **135**:387, 1942.
7. de Haan, J., Die Phagocytose als Ausdruck des Lebens der Leukocyten, Pfluger's Arch. **194**:448, 1922.
8. McCance, R. A., Renal function in early life, Physiol. Rev. **28**:331, 1948.
9. Jonxis, J. H. P., in Haemoglobin: Symposium, New York, Interscience Publishers, Inc., 1949, p. 261.
10. Mollison, P. R., and Cutbush, M., Bromsulphalein excretion in newborn, Arch. Dis. Childhood **24**:7, 1949.

Spanish Abstract

Actividad Fagocítica y Amiboidea de los Leucocitos del Recién Nacido

La escasa resistencia a la infección, característica del recíen nacido, es debida en gran parte a que el mecanismo humoral de defensa se encuentra incompletamente desarrollado como resultado de la falta de experiencia del organismo del niño para combatir la infección. Es posible, además, que a este factor se añada otra causa que contribuya a esta poca resistencia y es que sus leucocitos realicen una función imperfecta como parecen sugerir algunas peculiaridades en el comportamiento de los glóbulos blancos durante el período neonatal.

El recién nacido presenta además variaciones y fluctuaciones muy amplias en el número de glóbulos blancos y particularmente de los neutrófilos polimorfonucleares y pueden no tener relación aparente con la enfermedad y con la salud. Efectivamente, una cuenta blanca desusualmente alta que en niños más grandes indicaría la presencia de una infección, en el niño recién nacido se les encuentra sin ninguna evidencia de enfermedad, por otra parte, las infecciones que generalmente producen una leucocitosis marcada en adultos o niños, no siempre lo hacen en el recién nacido.

Estos hechos motivaron a los autores de este trabajo a hacer un estudio experimental de las funciones de los leucocitos del recién nacido en lo relativo a su capacidad fagocítica y motilidad amiboide comparándola con la de leucocitos de controles adultos, sus propias madres en algunos casos; usando granos de almidón para determinar la actividad fagocítica y cuantificando el porcentaje de células que presentaron morfología y movimientos amiboides.

Sus resultados les permiten afirmar que los leucocitos neonatales obtenidos de la sangre del cordón tienen una actividad fagocítaria y amiboide menor, comparada con la de los leucocitos maternos y de

otros individuos adultos, indicando una diferencia funcional inherente que está de acuerdo con diferencias similares y la inmadurez funcional encontrada en otros órganos y sistemas y que ha sido reportada por varios autores. Estas diferencias no dependen de un factor hormonal presente en la madre pues los movimientos amiboides y actividad fagocítica leucocitaria del niño recién nacido comparada con los de su propia madre y usando como control leucocitos de personas adultas no embarazadas, demostró obviamente que dichas características eran menos marcadas en los leucocitos del recién nacido que en ambos grupos mencionados y por otra parte, de que la anoxia sufrida "in vivo" por los leucocitos neonatales no modificó en forma irreversible su actividad fagocítica "in vitro" pues en los experimentos, ambos tipos de leucocitos tenían igual acceso a oxígeno y dada la anoxia fisiológica del feto y su supuesta mayor eficacia en utilizar un metabolismo anaeróbico, los del recién nacido debían de haber mostrado mayor actividad fagocítica.

Por otra parte, como ha sido demostrado por otros investigadores, la menor motilidad amiboide de los leucocitos no determina su poder fagocitario; en este mismo experimento sus autores encontraron también que no son fenómenos paralelos, pues mientras la disminución de la actividad amiboide de las células leucocitarias del niño se observó en una solución salina pura, en la cual tanto estas como los leucocitos de adulto apenas mostraron capacidad fagocitaria alguna, cuando se repitió dicha experiencia en un medio que contenía suero, en el cual ambos tipos de células eran indiferenciables en lo que respecta a su motilidad amiboidea, fué indudable la franca disminución de la actividad fagocitaria de los leucocitos neonatales comparada con la de los leucocitos adultos.

Finalmente, aunque los datos reportados en este estudio fueron obtenidos en condiciones artificiales subóptimas que probablemente no sean reproducidas "in vivo," sin embargo, representan una prueba objetiva de la inferioridad funcional de los leucocitos neonatales cuyo significado en relación con la exigua resistencia que ofrece el recién nacido a la infección es difícil de evaluar. Hasta nuevos estudios este informe servirá para llamar la atención acerca de la existencia de una diferencia biológica entre los leucocitos del recíen nacido y del adulto.

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OXIMETER STUDIES IN NEWBORN INFANTS DURING CRYING

By KLARA J. PREC, M.D.,* AND DONALD E. CASSELS, M.D.
Chicago

DURING a study of the arterial oxygen saturation in normal newborn infants a marked variation in saturation during crying was observed. Further observations indicated a relation between age and this variation in saturation, the pattern of response being quite different in young infants from the response to crying in those over a few days old. The purpose of this paper is to present a study of the influence of age on the change in oxygen saturation during crying in the newborn infant.

MATERIAL

The oxygen saturation of 135 full term infants ranging in age from 1½ hr. to 9 days and varying in weight between 2630 gm. and 4584 gm. was determined by the oximeter. All the babies had been examined after delivery and again on admission to the nursery and all were considered normal by the usual standards. Infants with delayed onset of respiration and those showing excessive amounts of mucus or amniotic fluid in the respiratory passages were excluded from the study.

METHOD

A single scale absolute reading oximeter, using the modified Coleman earpiece, was used. This apparatus has been shown by Wood[1,2] to give accurate determination of arterial oxygen saturation in ranges above 90% saturation, although increasing error is introduced in measuring lower saturation. Since this study is concerned with sudden changes in saturation rather than with absolute values the oximeter method is considered satisfactory for the purpose of the study. The adult earpiece, which fits the ear of most infants, was used. A few infants, for whom it was too large, could not be used. In a number of infants the duration of observation, 30 to 45 min., was sufficiently long to result in minor burns at the earpiece site, and although these readily healed, this precluded sequential observations in the same infant.

After a preliminary warming up period of 15 min. 3 saturation readings were taken while the infants were asleep. The infants were made to cry for 5 min. when similar determinations were again recorded, all during persistent crying. Between readings the ear was rendered bloodless and the IR (infrared) and R (red) readings were adjusted. In 28 subjects the same procedure was followed while oxygen was administered by mask, using a flow of 7 l./min. Analyses of samples drawn under the mask showed an oxygen content from 73 to 98.5% and CO_2 between 0.45 and 0.53%. Small oscillations of the galvanometer needle frequently made precise readings difficult. In such cases the mean of the upper and lower limits of these movements was used as the saturation value. During the observations on a given infant the amount of movement, the depth of sleep and the intensity of crying often varied. The mean of 3 consecutive saturation readings was believed to minimize this variation.

RESULTS

It was apparent at once that infants less than 4 days old reacted differently in respect to changes in oxygen saturation during crying than older infants. The subjects were therefore divided into two groups, the first including those up to 4 days of age and the

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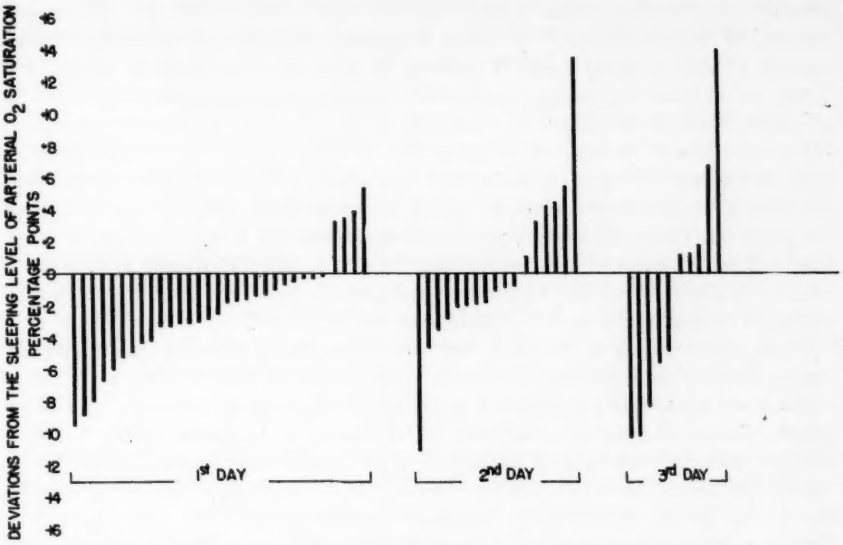

CHART 1. Changes of arterial oxygen saturation with crying in newborn infants during 1st 3 days of life. Zero line represents sleeping level. Decreases in saturation are charted below, increases above this line.

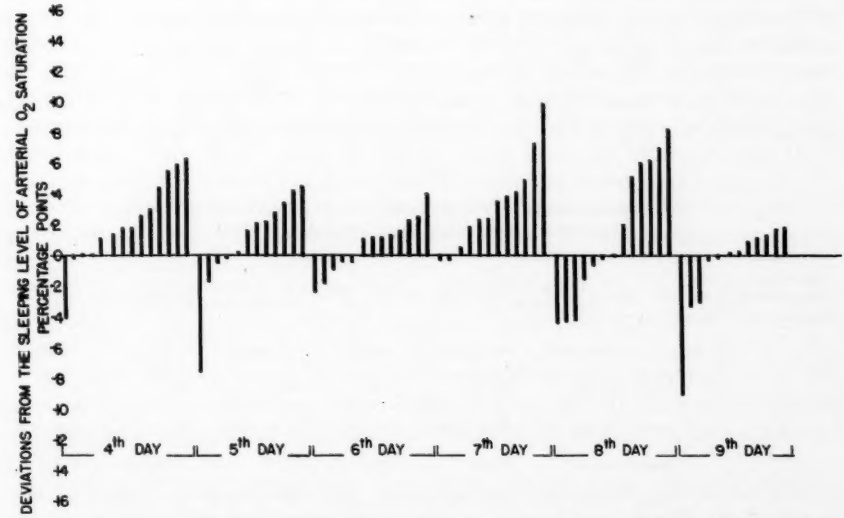

CHART 2. Changes of arterial oxygen saturation with crying in newborn infants between fourth and ninth day of life. Zero line represents sleeping level. Decreases in saturation are charted below, increases above this line.

second group including those 4 to 9 days old. One hundred thirty-five infants were studied, 59 in group I and 76 in group II. Of the 28 infants studied while breathing oxygen, 15 were in group I and 13 in group II. Using the mean sleeping value of each infant as the base line, charts 1 and 2 were constructed showing the direction of the deviation from the sleeping level caused by crying. Decreases in saturation are shown below the line and increases above the baseline. A comparison of the two groups on the basis of changes in oxygen saturation from the sleeping level would seem justified since the mean values of oxygen saturation during sleep were quite similar in the two groups. In group I the mean saturation during sleep was 94.94 with a range of 75% to 103%, and in group II it was 94.79% with a range of 87.5 to 102.6%. During sleep values of oxygen saturation lower than accepted normal values in adults were frequently observed, similar to the observation made by Crehan, Kennedy and Wood.[3]

Unlike the similarity of the mean saturation values during sleep, the mean saturation values observed during crying, 93.2% in group I and 96.1% in group II, are quite different. In group I this represents a decrease from the sleeping level of 1.7 percentage points, whereas in group II it represents an increase of 1.2 percentage points. The mean changes from the sleeping level during crying are small because in both groups they include increases and decreases, but the difference in the mean responses to crying in the two groups is large enough to be statistically significant ($t = 3.83$). The ranges of the individual decreases or increases in saturation due to crying varied little in the two groups, but there is a marked difference in the relative numbers of infants in each group who showed decreases or increases. During the first three days of life there was a marked tendency for the arterial oxygen saturation to decrease with crying (chart 1), while between the fourth and ninth day the saturation tended to increase with crying (chart 2). Of the 59 infants in group I, 39 (66.1%) showed decreased saturation with crying, 16 (27.1%) showed an increase and 4 (6.8%) showed no change or changes of less than 0.5 percentage points. Group II showed a trend in the opposite direction. Of the 76 infants in this group, only 16 (21.0%) showed a decrease in saturation due to crying, while 45 (59.2%) showed an increase and 17 (22.4%) showed no change. Thus, the individual results shown in charts 1 and 2 emphasize the difference between the two groups which was suggested by the mean saturation values. Crying during the first three

TABLE 1

CHANGES IN ARTERIAL OXYGEN FROM SLEEPING TO CRYING IN AIR AND WHILE BREATHING HIGH OXYGEN MIXTURES

Effect Due to Crying While Breathing Air	No. of Cases		Arterial O_2 Saturation Breathing Air, Per Cent		Percentage Points	Arterial O_2 Saturation Breathing Oxygen, Per Cent		Percentage Points
	28		sleeping	crying	change	sleeping	crying	change
Increase	12	mean	93.93	97.52	3.59	100.4	100.9	0.5
		range	91.3 – 97.8	93.9 – 100.4	1.2 – 6.8	97.9 – 104	98.4 – 103.6	0.6 – 1.3
Decrease	10	mean	96.59	92.93	3.66	99.63	97.87	1.76
		range	94.7 – 98.9	87.8 – 97.6	0.7 – 11.1	98 – 102.8	96 – 100.5	0.7 – 4.4
No change	6	mean	98.1	97.9	0.2	101.4	101.3	0.1
		range	95.2 – 100.3	94.9 – 100.5	0.2 – 0.5	98.9 – 104	98.7 – 103.6	0.1 – 0.7

days of life is associated with a decrease of arterial oxygen saturation in a large percentage of infants, although the magnitude of the decrease is frequently not great; between the fourth and ninth days few infants show this decrease, while the majority show increases in oxygen saturation during crying.

In an attempt to test the role of pulmonary function in the variations of oxygen saturation during crying, oxygen was administered by mask as previously described. The data of these observations are shown in table 1. In oxygen the saturation during sleep rose to 98 to 104%. Because of this high saturation, increases with crying, when they occurred, were slight. However, decreases during crying were similar in oxygen and in air, although of a somewhat smaller magnitude. Ten infants in this group showed decreases in saturation due to crying while breathing air and eight of these also showed a decrease while breathing oxygen. Four showed no change. Seven of 12 infants whose saturation increased while crying in air showed slight increases in oxygen and five showed no change. The trend of these changes was therefore similar in both oxygen and air.

Discussion

Little information is available concerning the circulatory and respiratory changes which take place in newborn infants during crying. The technical difficulties involved in obtaining such measurements are considerable and few reliable data are available. In respect to the circulation, the heart rate increases during crying, rates of 180/minute being observed. The blood pressure also increases, as shown by Woodbury.[4] Respiration during sleep in newborn infants is shallow, irregular and may be associated with arterial oxygen saturation below the normal adult or childhood range. Crying tends to deepen respiration and increase the minute volume of air inspired.[5,6]

Crying represents a deep inspiration followed by a prolonged expiration through a partially closed glottis. In most infants there is a certain amount of breathholding associated with the prolonged expiration. Crying necessitates considerable respiratory effort and requires active participation of accessory respiratory muscles during the inspiratory and expiratory phase. This is illustrated by observations made by Smith[7] who measured intrapulmonary pressures in newborn infants during inspiration against partial or complete obstruction. He found decreases in pressure of −40 mm. of water during struggling and crying in most infants. He noted that in infants who were less active, particularly during the first few hours of life, pressures were not so low, between −25 and −30 mm. He believes this is partly due to somnolence and low general irritability and partly due to inability to develop higher negative pressure because of weak thoracic forces. This thoracic force increases with age.

Most investigators[8–10] believe that the expansion of fetal lungs does not occur suddenly at birth, but that this process is gradual. Opinions differ in regard to the time required for full expansion, but if it is assumed that a few days are required it would be reasonable to expect scattered atelectatic areas throughout the newborn lung during this time. Normal oxygen saturation in an infant does not exclude the presence of such atelectatic areas since normal oxygenation is possible in the presence of large nonaerated portions of lung.[11]

Consideration of the available data suggests that the increase in tidal air and minute volume during crying could raise the oxygen saturation simply through an increase in alveolar oxygen tension. This appears to be the most likely explanation for the increase in oxygen saturation in the majority of infants of group II and in some of the infants

of group I. The expansion of previously nonaerated alveoli, caused by marked lowering of intrapleural pressure during the inspiratory phase of crying, does not seem to be a factor in raising saturation, since increases in oxygen saturation during crying were found more uniformly in the older age group in whom atelectatic areas in the lungs should be less common than in the younger group.

It is more difficult to understand the decreases of saturation with crying which occur most frequently during the first three days of life. Breath-holding under normal conditions can cause a decrease in arterial oxygen saturation, the degree depending on the alveolar oxygen tension.[12] However, an oxygen-enriched atmosphere abolishes this effect.[13] In the newborn, decreases of oxygen saturation occurred during crying in air as well as in high oxygen mixtures. It is very unlikely therefore that the decrease in oxygen saturation during crying was caused by breath-holding.

Assuming that small atelectatic areas are present in the lung of the newborn during the first few days of life, it is possible that increases of intrapulmonary pressure during the prolonged forceful expiration of crying might affect alveoli filled with air to a greater extent than nonaerated alveoli, and lead to a relatively greater increase of resistance to blood flow in the former. Cournand[14] believes that blood distribution through individual portions of the lung is governed by local mechanical conditions and that blood may be shunted away from regions where vascular resistance is increased. If during crying vascular resistance is greater in aerated areas, pulmonary blood flow through nonaerated areas should be increased and blood returning from the lungs would be incompletely saturated. More recent observations on pulmonary pressures during positive pressure breathing seem to indicate an increase of peripheral resistance in the pulmonary circuit as the result of increased alveolar pressures.[15, 16] No data are available comparing blood flow and peripheral resistance in aerated and nonaerated portions of the lung.

The third possible explanation for the observed decrease in oxygen saturation during crying, which was observed most frequently during the first three days of life, is the persistence of a fetal blood pathway from the right to the left heart such as the foramen ovale or the ductus arteriosus. It would seem unreasonable to consider seriously the ductus arteriosus in this respect, since if blood flow did occur from pulmonary artery to aorta this would have to pass in a retrograde way up the aorta into the carotid artery to affect the saturation as determined by the ear oximeter. It is generally assumed that physiologic closure of the foramen ovale takes place shortly after birth, this closure depending upon an increase of left atrial pressure due to increased return of blood from the functioning lung. The normal pressure gradient between the left and right atria during the first 10 days of life is not known. Cournand and Motley[17] recorded by catheterization pressures in the right and left atria and in the pulmonary veins in three subjects with interatrial septal defects, who were 5 months, 2 years and 5 years of age. The average mean auricular pressure gradient was 3 mm.Hg, with mean auricular pressures of 4.1 mm.Hg in the left auricle and 1.4 mm.Hg in the right auricle. They believe that shunting of blood from the right to the left auricle, particularly during increased activity, is a possibility in auricular septal defects in spite of the normal left to right pressure gradient. Although conditions in the newborn are not exactly analogous to the circumstances of interauricular septal defects, they are similar in that there is a potential opening allowing right to left flow, should the pressure gradient be appropriate, since anatomic closure is not immediate.

Brecher and Opdyke[18] examined the effect of normal and abnormal respiration on the

hemodynamics of dogs with experimental interauricular septal defects. They found that a decrease in intrathoracic pressure frequently resulted in a reversal of the normal left to right effective interauricular pressure gradient at the time of atrial systole. This occurred almost invariably during Muller's experiment, particularly in those animals whose initial left to right pressure gradient was small. Their evidence is inconclusive in regard to a gradient reversal during the Valsalva type of respiration. In four such experiments the left to right gradient decreased, but a gradient reversal occurred only in one normal closed chest dog.[19] In this dog, while the animal was actively using all the expiratory muscles, a progressive increase in intrathoracic pressure from the apneic level of 12 mm. saline to 115 mm. occurred. As a result, the effective right auricular pressure increased markedly to plus 40 mm., while the left decreased to minus 10 mm. The right auricular pressure was higher than the left during most of the cardiac cycle. This is the only instance on record where it has been shown that the interatrial pressure gradient can be reversed and maintained for an appreciable time during expiration. The authors suggest that this occurs only if the intrathoracic pressure is increased and maintained by a prolonged contraction of the expiratory muscles. It is possible therefore that in the newborn a gradient reversal occurs during the deep inspiration of crying and also during the forceful expiration, which is a type of Valsalva breathing and requires the active participation of all respiratory muscles over a prolonged period of time. The venous arterial shunt through the foramen ovale which is the result of a right to left interauricular pressure gradient could readily cause varying degrees of diminution of arterial oxygen saturation.

In considering these possible explanations of the observed decrease in oxygen saturation during crying in newborn infants, the authors suggest that a venous-arterial shunt through the foramen ovale is a probable explanation. The possibility of an intrapulmonary shunt has not been definitely excluded.

Summary

The arterial oxygen saturation was determined in 135 healthy newborn infants during sleep and while crying with a direct reading single scale oximeter. In the first group, consisting of infants from one hour and 30 minutes to 3 days of age, 66% showed a decrease of oxygen saturation with crying, 27% an increase and 6.8% no change. In the second group, which includes all infants between 4 and 9 days of age, 59% showed an increase in saturation with crying, 21% a decrease and 22.4% no change. In comparison, the mean results in these two groups are in the opposite direction. These changes are statistically significant. Twenty-eight infants were studied also while breathing oxygen (73%-98.5%), and the results compared with those in room air were found to show an identical trend.

It is concluded that increases in arterial oxygen saturation with crying, which occur most frequently in older infants, are probably due to an increase in alveolar oxygen tension secondary to improved pulmonary ventilation during crying.

The paradoxic decrease in saturation during crying, which was found in a large percentage of infants of the younger group, is suggestive of the presence of a transitory venous-arterial shunt. This shunt could be either through atelectatic areas of the lung or through the foramen ovale, which is only functionally closed and can open whenever the pressure in the right auricle exceeds the left auricular pressure. There is some available evidence to support the latter possibility.

ACKNOWLEDGMENT

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REFERENCES

1. Wood, E. H., and Geraci, J. E., Photoelectric determination of arterial oxygen saturation in man, J. Lab. & Clin. Med. **34**:387, 1949.
2. Wood, E. H., Single scale absolute reading oximeter, Proc. Staff. Meet., Mayo Clin. **25**:384, 1950.
3. Crehan, E. L., Kennedy, R. L. J., and Wood, E. H., Study of oxygen saturation of arterial blood of normal newborn infants by means of modified photoelectric oximeter: Preliminary report, Proc. Staff. Meet., Mayo Clin. **25**:392, 1950.
4. Woodbury, R. A., Robinow, M., and Hamilton, W. F., Blood pressure studies on infants, Am. J. Physiol. **122**:472, 1938.
5. Deming, Jean, and Washburn, A. H., Respiration in infancy. I. Method of studying rates, volume and character of respiration with preliminary report of results, Am. J. Dis. Child. **49**:108, 1935.
6. Deming, Jean, and Hanner, J. P., Respiration in infancy. II. Study of rate, volume and character of respiration in healthy infants during neonatal period, Am. J. Dis. Child. **51**:823, 1936.
7. Smith, C. A., and Chisholm, T. C., Intrapulmonary pressures in newborn infant, J. Pediat. **20**:338, 1942.
8. Farber, S., and Wilson, J. L., Atelectasis of newborn: Study and critical review, Am. J. Dis. Child. **46**:572, 1933.
9. Solis-Cohen, L., and Bruck, S., Roentgen examination of chest of 500 newborn infants for pathology other than enlarged thymus, Radiology **23**:173, 1934.
10. Dunham, E. C., and D'Amico, M., Roentgenographic study of thoraces of newborn infants, Yale J. Biol. & Med. **6**:385, 1934.
11. Smith, C. A., and Kaplan, E., Adjustment of blood oxygen levels in neonatal life, Am. J. Dis. Child. **64**:843, 1942.
12. Ferris, E. B., Engel, G. L., Stevens, C. D., and Webb, J., Voluntary breathholding. III. Relation of maximum time of breathholding to oxygen and carbon dioxide tensions of arterial blood, with note on its clinical and physiological significance, J. Clin. Investigation **25**:734, 1946
13. Prec, Klara J., Unpublished data.
14. Cournand, A., Some aspects of pulmonary circulation in normal man and in chronic cardiopulmonary diseases, Fourth Walter Wile Hamburger Memorial Lecture, Institute of Medicine of Chicago, Circulation **2**:641, 1950.
15. Barach, A. L., and others, Studies on positive pressure respiration. I. General aspects and types of pressure breathing. II. Effects on respiration and circulation at sea level, J. Aviation Med. **17**:290, 1946.
16. Carr, D. T., and Essex, H. E., Certain effects of positive pressure respiration on circulatory and respiratory systems, Am. Heart J. **31**:53, 1946.
17. Cournand, A., and others, Recording of blood pressure from left auricle and pulmonary veins in human subjects with interauricular septal defect, Am. J. Physiol. **150**:267, 1947.
18. Brecher, G. A., and Opdyke, D. F., Effect of normal and abnormal respiration on hemodynamics of experimental interatrial septal defects, Am. J. Physiol. **162**:507, 1950.
19. Opdyke, D. F., and Brecher, G. A., Effect of normal and abnormal changes of intrathoracic pressure on effective right and left atrial pressures, Am. J. Physiol. **160**:556, 1950.

SPANISH ABSTRACT

Estudios Oximétricos Durante el Llanto en el Recién Nacido

Al estudiar la saturación arterial de oxígeno en el recién nacido normal, se encontró que había variaciones marcadas de ella durante el llanto. Observaciones posteriores indicaron una relación entre la edad y esta variación, siendo el tipo de respuesta muy diferente en niños recién nacidos pequeños, de la de los que tenían algunos días de edad. El propósito de este artículo es presentar un estudio sobre la influencia que la edad tiene sobre la saturación de oxígeno durante el llanto, en el recién nacido.

Se determinó por el oxímetro la saturación de oxígeno de 135 niños a término cuya edad varió desde una y una y media horas, hasta 9 días, con pesos variables entre 2.630 gramos y 4.584 gramos. Los niños que tuvieron iniciación retardada de la respiración y aquellos con cantidades excesivas de moco o de líquido amniótico en el tracto respiratorio fueron excluídos del trabajo.

Se encontró que los niños de menos de 4 días de edad reaccionaban diferentemente respecto a los cambios de la saturación de oxígeno durante el llanto, que los niños mayores. Por lo tanto se tomaron dos grupos, el primero incluyó aquellos hasta de 4 dias de edad y el segundo a los que tenían de 4 a 9 días. Hubo 59 en el grupo I y 76 en el grupo II.

Usando las cifras encontradas durante el sueño como una línea base, se construyeron gráficas que mostraron las desviaciones sobre este nivel causadas por el llanto, presentando a la disminución en la saturación por un descenso por abajo de la línea y al aumento por un ascenso sobre ella. Los valores durante el sueño fueron similares en los dos grupos, pero las cifras encontradas durante el llanto en el grupo I representan una disminución sobre el nivel basal 1.7 puntos por ciento; mientras que en el grupo II representan un aumento de 1.2 puntos por ciento, diferencia pequeña pero de significación estadística. Durante los primeros tres días de vida hubo tendencia a disminuir la saturación arterial de oxígeno con el llanto, mientras que entre el cuarto y el noveno día la saturación arterial de oxígeno tendió a aumentar por esta misma causa.

Se sugiere como explicación de este hecho para el grupo II, que el aumento en el volumen de aire circulante durante el llanto aumentaría la saturación de oxígeno al hacer crecer la tensión de este gas en el alveolo.

En cuanto a la disminución observada en el grupo I se exponen 3 hipótesis: Una es que la detención de la respiración durante el llanto haya provocado el descenso de la saturación. Otra que habiendo pequeñas áreas de atelectasia en los pulmones del recién nacido durante los primeros días de vida, al aumentar la presión intrapulmonar durante la expiración prolongada, se produce una mayor resistencia para la circulación sanguínea en los alveolos con aire; y la tercera explicación posible sería la persistencia de circulación, entre corazón derecho e izquierdo, por un paso fetal, tal como el agujero oval o el conducto arterioso.

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OBSTRUCTION OF DUODENUM IN THE NEWBORN INFANT DUE TO ANNULAR PANCREAS

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DUODENAL obstruction in the newborn requires prompt recognition and treatment. One of the causes of such obstruction is complete encirclement of the duodenum by a ring of pancreatic tissue.

Many articles have been written on the subject of annular pancreas, but this anomaly has received scant attention in the pediatric literature. The reason is probably that the majority of individuals with an annular pancreas do not develop symptoms until they have reached adult life, or may never develop any difficulty and the condition is an incidental autopsy finding.

A recent review of the literature by Payne[1] revealed 57 cases, and Ravitch[2] has reported three more. Twenty-one of these patients have been treated surgically. Only 5 of the 60 cases were newborn infants[2-5] and these were all in the surgically treated group. The present authors have seen four infants with duodenal obstruction due to an annular pancreas in the last 20 months. The purpose of this report is to add these 4 cases to the 5 previously reported, and to review the 9 cases treated in the neonatal period in an effort to find out if there is some way of arriving at a correct preoperative diagnosis. The treatment of the four cases herein reported will be discussed.

CASE REPORTS

Case 1, B.M. A white female infant was transferred to the pediatric service on the 3rd day of life because of persistent vomiting. Pregnancy, labor and birth were uncomplicated and at birth she appeared normal, birth weight 2490 gm. All attempts at feeding in the nursery resulted in forceful vomiting with the vomitus containing curdled milk but never any bile or blood. Within the 1st 3 days of life only one meconium and one brown stool were passed.

On physical examination she appeared well-developed and poorly nourished; temperature, pulse and respiratory rate were normal and except for slight jaundice examination findings were within normal limits. Laboratory data revealed no abnormalities other than an NPN of 68.2 mg./100 cc. which was interpreted as evidence of dehydration. A scout film of the abdomen revealed 2 large gas shadows interpreted as being within the stomach and duodenal bulb.

On 2nd hospital day, an exploratory laparotomy revealed a constriction of 2nd portion of duodenum proximal to the ampulla of Vater by an annular pancreas. Encircling pancreas was biopsied and a gastroduodenostomy was performed. Postoperatively the child did well except for minimal vomiting on 12th hospital day. She was discharged apparently well on the 27th hospital day. She has been followed for 20 mo. and growth and development have been normal.

Case 2, B.K. A white female infant was transferred to Babies and Children's Hospital on 6th day of life with a history of persistent vomiting since birth. Pregnancy, labor and birth had been uncomplicated, birth weight 2405 gm. It was noted that the child vomited greenish material immediately after birth. Attempts to feed the patient resulted in persistent vomiting which was frequently bile-stained. Physical examination on admission revealed a fairly well-nourished, mongoloid appearing infant who was acutely ill. Temperature, pulse and respiratory rate were within normal limits.

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Skin was jaundiced and there were petechiae over abdomen and thighs. Abdomen was distended and frequent peristaltic waves were noted over the upper abdomen. During the examination the child vomited coffee ground material and passed a dark brown stool which gave a strongly positive benzidine reaction. Laboratory findings were negative except for an icteric index of 160 u. A flat plate of the abdomen revealed 2 large oval gas shadows interpreted as being within the stomach and duodenal bulb region, the remainder of the abdomen being devoid of gas.

After correcting dehydration, a laparotomy revealed an annular pancreas obstructing the second portion of the duodenum. A duodenoduodenostomy and a gastrostomy were performed. Postoperatively the patient's course was fairly good for 1st 7 days in spite of increasing jaundice. On 8th day she began to vomit intermittently and on 11th day she died suddenly.

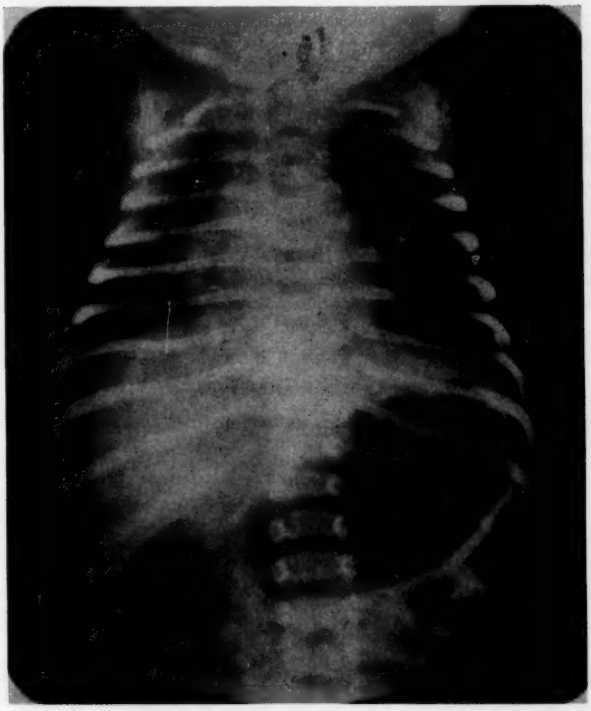

FIG. 1. Note "double bubble" sign, gas in lower bowel and aspiration pneumonitis.

Autopsy revealed an annular pancreas constricting the duodenum 2 mm. below entrance of common bile duct and a small probe could be passed through the constriction. Intramural portion of common duct was also surrounded by pancreatic tissue and was markedly narrowed, probably accounting for the jaundice. Cause of death was occlusion of trachea and main stem bronchi by numerous mucous plugs.

Case 3. D.S. A white male infant was admitted to Babies and Children's Hospital at age of 10 days, because of vomiting, weight loss and dehydration. Feedings were begun 36 hr. after birth with 5% dextrose in water, which he tolerated well. On 3rd day of life a dilute evaporated milk formula was offered and vomiting was noted 10 to 15 min. after feeding. Vomiting persisted after each feeding and was generally bile stained. Stools consisted of meconium and were small and infrequent. Physical examination on admission revealed a dehydrated, mongoloid appearing infant weighing 2500 gm. with normal temperature, pulse and respiratory rate. Upper abdominal distention with peristaltic waves traversing the abdomen from L to R were noted and no pyloric tumor was

palpable. Mongolism was evident by facies, severe hypotonia, hyporeflexia and speckled irides; however, no simian lines were noted. Laboratory findings were within normal limits. Flat plates of the abdomen taken prone, erect, and in L lateral decubitus position (after instilling air 30 cc. into stomach by gavage tube) revealed typical "double bubble" sign of duodenal obstruction, and scattered gas shadows throughout small intestine (Fig. 1). A barium enema revealed that the colon had completely rotated into its normal position. After correction of the dehydration, gastric distention and recovery from aspiration pneumonia, an exploratory laparotomy was performed at age of 17 days. Dilatation of the proximal duodenum was noted which abruptly narrowed in region of pancreas and pancreatic tissue was identified completely encircling second portion of duodenum. The lesion was so obvious that no dissection was necessary, and a by-pass duodenojejunostomy was performed. Oral feedings were begun on 3rd postoperative day with intermittent vomiting occurring for 14 days. A Monilia infestation of mouth was noted at this time and with therapy the thrush subsided. Vomiting abated, and patient has subsequently been asymptomatic.

Case 4, G.S. A white female infant was transferred to Babies and Children's Hospital on the 7th day of life because of persistent vomiting. Pregnancy, labor and birth were uncomplicated, birth weight 2400 gm. Feedings were begun after 36 hr. and vomiting was noted to occur 15 to 60 min. after feedings. Vomiting became progressive and severe, and stools were noted to consist only of several small lumps of meconium. Barium given by mouth at the other hospital was said to reveal a duodenal obstruction. Physical examination on admission revealed a moribund, severely dehydrated infant who failed to respond to painful stimuli. There was distention of upper abdomen. Respirations were barely perceptible with a rate of 10/min., indicative of the severe metabolic alkalosis which existed. Corrective measures were promptly instituted and, 16 hr. after admission, the CO_2 content had fallen to 62 vol. % and pH to 7.57 and serum chloride had been raised to 94 mEq./l. Exploratory laparotomy revealed an annular constricting ring of pancreatic tissue, obstructing 3rd portion of duodenum 1 cm. to R of ligament of Treitz. Duodenojejunostomy was chosen as the procedure of choice for reasons discussed under treatment. Postoperative course was uneventful.

Embryology and Etiology

Embryologically[6] the pancreas develops as two distinct entodermal diverticuli, known, respectively, as the dorsal and ventral *anlage*. The dorsal *anlage* forms the future body and tail of the pancreas and its duct empties into the duodenum just above the orifice of the common bile duct. This forms the accessory duct of Santorini which usually anastomoses with the ventral duct or may become completely atretic (Fig. 2).

The ventral *anlage* appears in the form of a diverticulum from the primitive bile duct and forms the major part of the pancreatic head and uncinate process, usually draining either into the duodenum close beside or directly into the ductus choledochus. The ventral duct usually becomes the major outflow duct for pancreatic secretions, the duct of Wirsung. Normally at about the sixth week of fetal life the two portions meet and fuse to form the adult-shaped pancreas. It is at this stage of development that the anomaly is thought to arise.

The annular portion of the pancreatic substance has all the histologic characteristics of a normal pancreas. It contains islets as well as acinar tissue. The ducts for the external secretions have been the subject of considerable investigation. They may be rudimentary

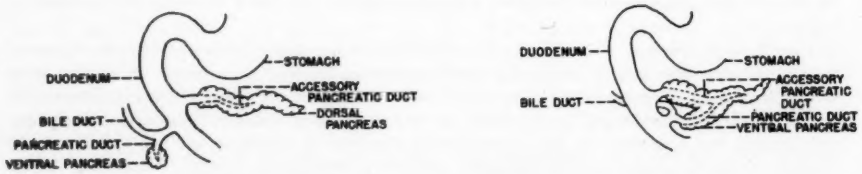

Fig. 2. A. Pancreas of human embryo of 5 wk. (Kollman). B. Pancreas of human embryo at end of 6th wk. (Kollman). Courtesy, *Gray's Anatomy*.

and may run from the anterior part of the ring towards the left to join the main pancreatic duct. However, it is more customary for the annular part of the pancreas to be traversed by a major duct which begins anteriorly, runs to the right, then curves around laterally and posteriorly, finally to join either the common bile duct or main pancreatic duct. In some of these cases the lower portion of the common duct passes through the posterior portion of the annular pancreas and is obstructed either by constriction or angulation.

This condition was first described by Tiedemann in 1818[7] and given the name "ring or annular pancreas" by Ecker in 1862.[8] Three theories have been suggested for this anomaly.

1. Failure of the dorsal and ventral diverticuli to unite as they usually do, and failure of rotation of the ventral *anlage* to its normal posterior position, resulting in pancreatic

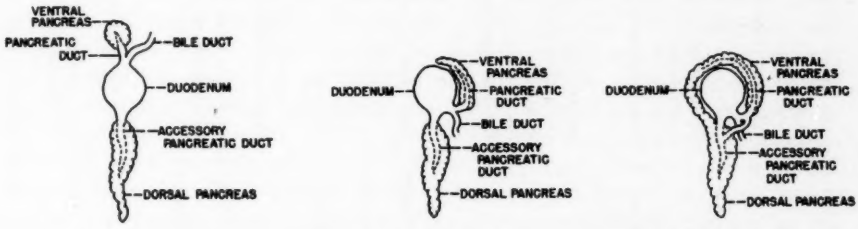

FIG. 3. Diagrammatic representation of mode of development of annular pancreas. Free end of ventral pancreatic anlage becomes fixed so that during its subsequent migration, with rotation of duodenum toward dorsal anlage it is drawn out. With fusion as shown at right, it comes to surround duodenum (after Lecco).

tissue on either side of the duodenum. With growth, the bowel becomes encircled by glandular tissue.

2. Lecco[9] believes that the anomaly owes its origin to the fact that the tip of the ventral *anlage* becomes adherent to the duodenal wall and in its normal migration and duodenal rotation it is stretched to form the ring (Fig. 3).

3. Weissberg feels that it is simply an unusual overgrowth of one of the pancreatic ducts.

Whichever theory is correct, it is interesting to speculate on the relationship of the encircling ring of pancreas to the stenoses and atresias which are the real factors producing the symptoms. Another finding in these cases which is difficult to explain is the position of the ring. In one case it was high on the second portion of the duodenum, in two, it was low on the second portion below the ampulla of Vater, and in one it was around the middle of the third portion of the duodenum.

DIAGNOSIS

Clinically the diagnosis of high intestinal obstruction should be considered whenever persistent vomiting occurs after the initiation of feedings. Classically in duodenal obstruction persistent vomiting, upper abdominal distention, visible peristaltic waves, decrease in size and frequency of meconium stools, progressive weight loss and dehydration are all present. The typical roentgenographic picture is the so-called "double bubble" sign produced by the dilated and radiolucent stomach and proximal dilated segment of duodenum. Barium studies should be avoided, as the instillation of air into the stomach

TABLE 1

Author	Sex	Type of Vomiting	Presence of Bile in Vomitus	Presence of Meconium Stools	Jaundice	Associated Anomalies	Type of Operation	Duodenal Obstruction	Results
Vidal 1905	F	Shortly after feedings	Yes	Yes	No	No	Posterior gastro-enterostomy	Atresia	Well—6 mo. later
Gross 1942	F	Projectile after each feeding	No	Yes	No	Incomplete rotation of colon	Duodenojejunostomy	Marked stenosis	Well—16 mo. later
Burger 1949	F	Persistent vomiting	Yes	Yes	Yes	No	(a) Pancreatic resection (b) Heinke-Mikulicz on duodenum	Atresia	Died—9th day post-operative, no autopsy
Ravitch Case 2 1950	F	At frequent intervals	Yes	Yes	No	No	Duodeno-jejunostomy	Marked stenosis	Well—20 mo. later
Ravitch Case 3 1950	M	3 hr. after feedings	Yes	No	Yes	(a) Incomplete rotation of colon (b) Portal vein anterior to duodenum (c) Small bowel mesentery unattached	Gastro-duodenostomy	Atresia	Well—2½ yr. later
Case 1 B.M.	F	Forcefully, shortly after feedings	No	Yes	No	No	Gastro-duodenostomy	Atresia	Well—20 mo. later
Case 2 B.K.	F	Persistent vomiting	Bile and blood	Yes	Yes	(a) Mongolism (b) Incomplete rotation of colon	Duodeno-duodenostomy	Marked stenosis	Died—11th day post-operative, bronchial obstruction
Case 3 D.S.	M	Shortly after each feeding	Yes	Yes	No	Mongolism	Duodeno-jejunostomy	Marked stenosis	Well—6 mo. later
Case 4 G.S.	F	After each feeding	Yes	Yes	No	No	Duodeno-jejunostomy	Atresia	Well—6 mo. later

will yield equally satisfactory information without the danger of barium in the bowel segment proximal to the obstruction. If the history and physical findings indicate high intestinal obstruction and the abdominal film does not show the "double bubble," air studies can be done by first aspirating the gastric contents and then injecting 30 cc. of air into the stomach via gavage tube. In the authors' experience this procedure just prior to prone, upright and decubitus films has been very satisfactory in demonstrating the "double bubble."

The above-mentioned findings are common to all duodenal obstructions regardless of the etiology. In an effort to ascertain whether a clinical diagnosis of annular pancreas could be made preoperatively the nine cases reported and treated in the neonatal period have been reviewed (table 1).

Only two of the infants were males and all were of the white race. Here again as in congenital atresia of the bile ducts the colored race is evidently rarely effected.[10] Visible peristalsis was seen in 4 of the 9 cases. The roentgenographic findings were indicative only of duodenal obstruction, differing in no way from the picture seen in obstruction from other causes. Gas shadows in the small intestine distal to the lesion depend upon the completeness of the obstruction. Gas was seen in the colon of one infant with a complete atresia and this was probably introduced by an enema. Jaundice was present in three cases. In Burger's case, no explanation for the jaundice was given. In Ravitch's case, it was felt to be due to back pressure in the duodenum. In Case 2 reported here, there was a stenosis of the common duct where it traversed the annular pancreas. Enough bile got into the intestine so that it was evident in the vomitus and stools but autopsy revealed a marked narrowing of the distal common duct.

The finding of associated mongolism in 2 of the 4 cases is of interest, but no explanation can be offered. Perhaps the defects that give rise to the clinical syndrome of mongolian idiocy occur at the same time in fetal life as do those causing an annular pancreas.

This study indicates that there are no criteria upon which it is possible to make a definite preoperative diagnosis of duodenal obstruction due to annular pancreas. Even if there were, operative intervention would be necessary to relieve the obstruction but a great deal of operative time could be saved if the cause was known before surgery.

Treatment

There have been in the surgical literature numerous discussions as to the best surgical approach for the correction of this anomaly. The direct attack on the encircling ring of pancreas has been advocated and several cases in adults have been successfully treated using this method. In Burger's case, the annular portion of the pancreas was removed and was followed by a Heincke-Mikulicz procedure on the stenosed duodenum. This case resulted in a fatality; however, the death could not be directly attributed to the type of operative procedure. At present the majority of surgeons seem to favor a by-passing procedure and the authors' experience leads them to believe that this is the treatment of choice for several reasons.

As has been pointed out by several investigators there is a definite risk of cutting a major pancreatic duct with subsequent fistula formation. In none of the nine patients would removal of the encircling ring suffice as there was a definite stenosis of the duodenum in four and a complete atresia in five. Therefore, one is faced not only with an

annular pancreas but also with a stenosed or atretic duodenum. Ladd,[11] Glover and Barry[12] and others have emphasized and demonstrated the value of a short-circuiting procedure in duodenal atresias and stenoses.

Furthermore, it was noticed that in all four patients the encircling pancreatic tissue was actually embedded in the duodenal wall. Removal of the annular pancreas under these circumstances may lead to a considerable amount of unnecessary bleeding with the real danger of damaging vital structures in this region. Autopsy of the patient in this series who died revealed that the aberrant pancreatic tissue was embedded in the wall of the duodenum and the removal would have involved resection of a portion of the duodenum. It was also noted that the ampulla of Vater was only 2 mm. away from the constricted area and a plastic procedure of any type might well have occluded the common duct. It has not been demonstrated that there is any constant relationship between the position of the annular pancreas and the site of the opening of the bile ducts into the duodenum and it therefore would follow that this is another strong argument against a direct attack on this area.

As there are no definite criteria for making a positive preoperative diagnosis of annular pancreas, the surgical approach is the same as for duodenal obstruction from any cause. Ladd[13] in 1932 described and illustrated this procedure and Glover and Barry[12] have recently reviewed and elaborated it. The colon is examined for malrotation and is then freed from its secondary attachments on the right and retracted to the left side of the abdomen. This exposes the entire duodenum. The lateral and inferior attachments of the duodenum are severed and the duodenum mobilized. At this point in three cases, the annular pancreas was recognized and a short-circuiting procedure decided upon. In Case 1 a gastroduodenostomy was done because the lesion was high on the duodenum. In Case 2 a duodenoduodenostomy was done because full mobility of the duodenum allowed this short by-pass. In Case 3 the annular pancreas was so large and evident that no dissection was necessary to recognize it. The duodenum was not disturbed and the jejunum was brought up anterior to the colon and anastamosed to the distended duodenum. The last of this series, Case 4, had a duodenojejunostomy because the lesion was in the third portion of the duodenum.

It should be remembered that in these cases as well as in all cases of obstruction in newborn infants, the entire intestine should be examined to rule out other areas of stenosis or atresia.

The decision as to what type of short-circuiting procedure should be done is dictated by the existing anatomic conditions. The by-pass should be as short as possible and the anastomosis should be made to the distended duodenum as close to the constricted area as possible. This allows for more effective drainage of the duodenum. Occasionally, the annular pancreas will be so high on the duodenum or the duodenum so thin that a gastroenteric anastomosis may be preferable.

Summary

Four cases of duodenal obstruction in the neonatal period caused by an annular constricting pancreatic ring are reported. These cases and the five others previously reported by different authors have been reviewed. Criteria were not found in this group of cases by which a definite preoperative diagnosis could be made. The etiology, embryology and treatment of this condition in infants have been discussed.

References

1. Payne, R. L., Annular pancreas, Ann. Surg. **133**:754, 1951.
2. Ravitch, M. M., and Woods, A. C., Annular pancreas, Ann. Surg. **132**:1116, 1950.
3. Vidal, E., Quelques cas de chirurgie pancréatique, Proces-Verbal Assoc. franç. de chirurgie **18**: 739, 1905.
4. Gross, R. E., and Chisholm, T. C., Annular pancreas producing duodenal obstruction, Ann. Surg. **119**:391, 1910.
5. Burger, R. E., and Alrich, E. M., Annular pancreas: Report of case, South. Surgeon **15**:83, 1949.
6. Gray's Anatomy, edited by W. H. Lewis, ed. 24, Philadelphia, Lea & Febiger, 1942, p. 1012.
7. Tiedemann, F., Deutsch Arch. Physiol. **4**:403, 1818.
8. Ecker, A., Malformations of pancreas and heart, Ztschr. f. rat. Med. **16**:354, 1862.
9. Lecco, T. M., Sur morphologie des pancreas annulare, Sitzungsb. d. wein Aked. d. Wissensch. **119**:391, 1910.
10. Gerrish, E. W., and Cole, J. W., Surgical jaundice in infants and children, Arch. Surg. **63**:529, 1951.
11. Ladd, E. W., Congenital duodenal obstruction, Surgery **1**:878, 1937.
12. Glover, D. M., and Barry, F. McA., Intestinal obstruction in newborn, Ann. Surg. **130**:480, 1949.
13. Ladd, W. E., Congenital obstruction of duodenum in newborn, New England J. Med. **206**:277, 1932.

Spanish Abstract

Obstrucción Ducdenal en el Recién Nacido Debida a Pancreas Anular

La revisión bibliográfica de las obstrucciones duodenales demuestra 57 casos debidos a malformación pancreática cuyo tejido forma un anillo alrededor del duodeno. De estos casos, 5 correspondieron a recién nacidos y los autores presentan 4 más haciendo una revisión clínica, patológica y terapeútica de todos los casos. Es probable que no obstante ser un padecimiento congénito, no se manifieste frecuentemente sino hasta la edad adulta y aun puede permanecer silencioso y ser un hallazgo de autopsia.

De estos 9 casos 7 eran del sexo femenino, su sintomatología fundamental era de vómitos persistentes, a veces postprandiales inmediatos o mas tardios, en proyectil, a intervalos frecuentes; en 7 enfermos contenían bilis, en uno de ellos mezclada con sangre y el restante no tenía ni una ni otra cosa, 4 enfermos tenían ondas peristálticas visibles en el epigástrio. Solo un caso no tuvo evacuaciones de meconio y tres tenían simultáneamente ictericia. Cuatro casos presentaron anomalias asociadas, en tres existía rotación incompleta del colon con mongolismo en uno de ellos; otro tenía además una vena porta situada adelante del duodeno y el mesenterio del intestino delgado era flotante y el cuarto caso exclusivamente mongolismo. La lesión anatómica duodenal fué de estenosis pronunciada en 4 casos y en el resto existía una verdadera atresia.

El estudio radiológico del tránsito gastrointestinal presenta la imagen de la "doble burbuja," ya sea en placa simple o si necesario, inyectando aire en cavidad gástrica después de haber vaciado su contenido por la misma sonda, no siendo necesario usar bario, por otra parte peligroso, ni tomar placas en decúbito dorsal, ventral, o de cabeza. El contorno de una de las burbujas es del estómago y la otra corresponde al duodeno; no es por consiguiente una imagen característica sino simplemente de obstrucción duodenal por cualquier causa ya sea completa, o incompleta, si es que simultáneamente existe aire en el resto del intestino.

La patogenia de los síntomas se explica bien por las anomalías anatómicas: vómitos biliosos, ausencia de evacuación no meconial, y la ictericia por estenosis en la porción intraparietal del colédoco.

Se colige por las consideraciones anteriores que es imposible hacer el diagnóstico preoperatorio de la malformación pero es decisivo para su terapeútica el diagnóstico de obstrucción duodenal quirúrgica.

La experiencia de los casos reportados favorece el tratamiento quirúrgico haciendo una duodeno-yeyuno-anastomosis, o gastroduodeno o duodeno-duodeno anastomosis y no la incisión del anillo de tejido pancreático que rodea al duodeno, primero, porque se ha visto que dicho tejido está frecuentemente embebido en la pared duodenal misma, segundo, por la frecuencia de atresia o estenosis duo-

denal en si como causa de la obstrucción y tercero, por la imposibilidad de saber a que distancia del anillo pancreático desemboca el coledoco y el peligro de lesionarlo así como el conducto de Wirsung. El tipo de anastomosis dependerá de la altura que en el duodeno se encuentre el anillo pancreático y la regla de que entre mas corta sea la parte de duodeno que se deja fuera del tránsito intestinal los resultados son mejores, así pues, si aquel es muy alto debe comunicarse estómago con duodeno, si esta bajo, duodeno con duodeno, o duodeno con yeyuno si el anillo es aún más bajo.

De los 9 casos analizados 7 fueron curados por uno u otro tipo de anastomosis, y estaban bien de 6 meses a 2½ años después de la operación; dos murieron, uno por obstrucción bronquial postoperatoria y el otro no se supo la causa.

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CHRONIC ULCERATIVE COLITIS

Case Report in a Newborn Infant

By SAMUEL L. BERANBAUM, M.D., AND ROBERT J. WALDRON, M.D.
New York City

CHRONIC ulcerative colitis in children is not uncommon. Of 871 cases at the Mayo Clinic reviewed by Jackman et al.,[1] 10.9% were children. Of these 95 cases, three had an onset of the disease within the first year of life. Hart[2] reported a case in the newborn with evidence of perforation, which was later shown by postmortem examination to be due to chronic ulcerative colitis.

This case report is presented as another beginning soon after birth, with roentgenographic studies of the colon. Although other reports of the disease in infancy are well documented, this report is the first in the newborn with complete roentgenographic studies.

REPORT OF CASE

At the age of 21 days, this white Italian male was admitted for the first time to University Hospital with the chief complaint of vomiting.

The present illness began 3 days after birth when it was noticed in the nursery that the infant began to vomit part of or all of its feedings. At the same time the infant became constipated so that enemata were necessary to obtain bowel movements. On one occasion, a small amount of blood was present in the stool. The infant was discharged from the nursery on the 5th day after birth on an evaporated milk, boiled water, dextrin-maltose-dextrose formula, but again at home he proceeded to have vomiting spells. The vomiting was never projectile. After the use of an antispasmodic before each feeding, the vomiting was controlled. Two days before admission date, the infant began to vomit again and now it was noticed that abdominal distension was present.

The family history is noncontributory.

Past history was unrevealing. The pregnancy was uneventful. The infant was a full term spontaneous delivery after a 2 hr. labor period and weighed 3943 gm. at birth.

Admission physical examination revealed a temperature of 38.4°C., pulse 100/min., respiration 44/min. The admission weight was 3.5 kg.

The infant did not appear acutely ill and the only positive physical findings at this time were abdominal distension and some prominence of the superficial veins of the abdominal wall.

Laboratory work on this admission revealed: RBC 3.45 million/cmm.; Hgb. 10.8 gm./100 cc.; WBC 17 thousand/cmm. with 34 neutrophiles; 36 lymphocytes, 12 monocytes, 15 metamyelocytes and 3 myelocytes of the neutrophilic type. An admission CO_2 combining power was 16.8 mEq./l. Seven stool cultures for enteric pathogens were negative. The erythrocyte sedimentation rate was 33 mm./hr. corrected.

Roentgenographic Examination (see Figs. 1 and 2): 1. Roentgenographic examination of the thorax showed no cardiac or pulmonary abnormalities and scout films of the long bones showed no gross abnormalities.

2. An initial scout film of the abdomen showed moderate gaseous distension of the intestines.

3. Colonic studies by barium enema and meal by mouth showed multiple mucosal irregularities and ulcerations throughout ascribable to ulcerative colitis. The colon was tubular in its entire course with absent haustrations.

Course in the Hospital: In the first part of the infant's stay in the hospital, it was considered that the infant had a small bowel obstruction. The infant passed small amounts of stool, consisting

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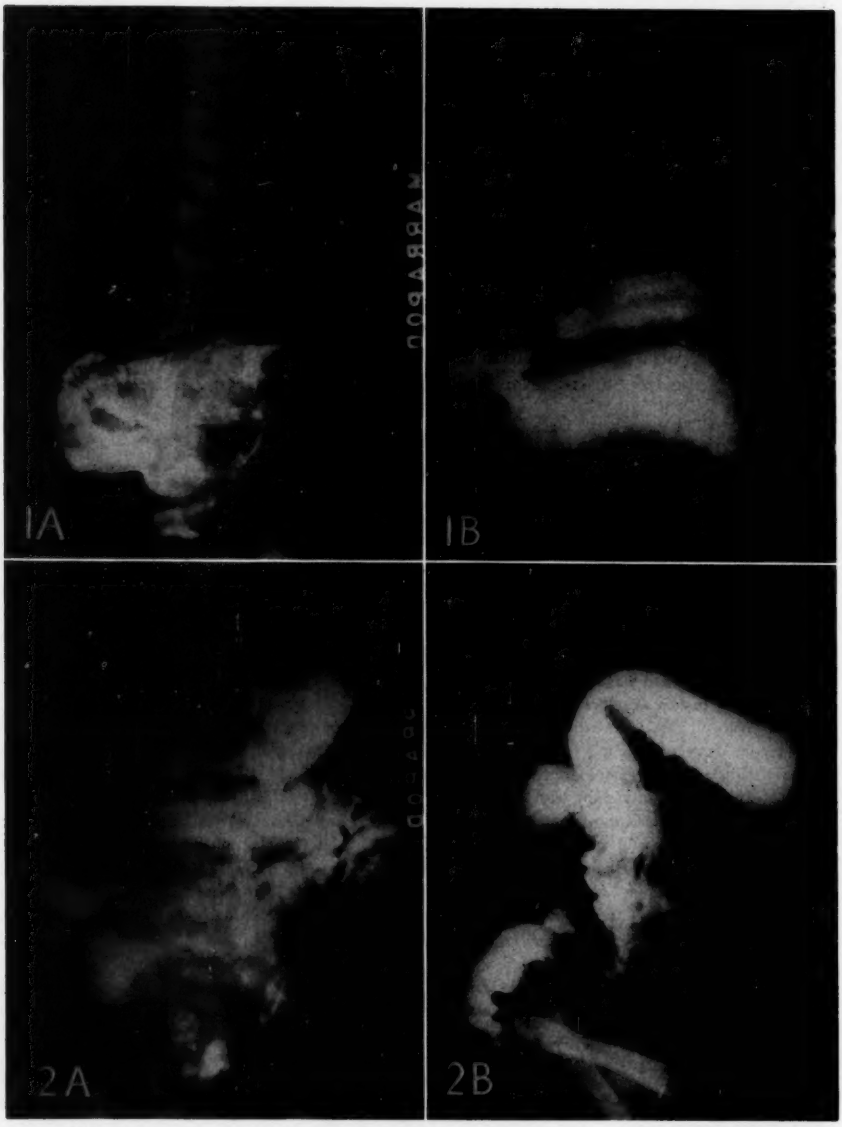

FIG. 1A and B. Colon shows multiple irregularities of mucosal pattern with multiple small ulceration. Patient was 24 days old at this time.

FIG. 2A and B. Colon visualized by meal by mouth shows tubularity throughout with absence of haustration.

of black slimy material, which gave a negative reaction to the guaiac test. The abdomen remained distended and no bowel sounds were heard. Since the consensus of surgical opinion was that this was a small bowel obstruction, a laparotomy was performed on the 6th hospital day.

At operation, the terminal ileum, cecum, ascending colon and part of the transverse colon showed a thick gut wall which was extremely friable and considerably inflamed. Following minimal manipulation of the intestine at operation, a perforation was inadvertently made into the cecum and just superior to that point in the ascending colon. The cecal perforation was closed and the ascending colon perforation was utilized for drainage.

Postoperatively the infant was given antimicrobial agents and supportive therapy, including

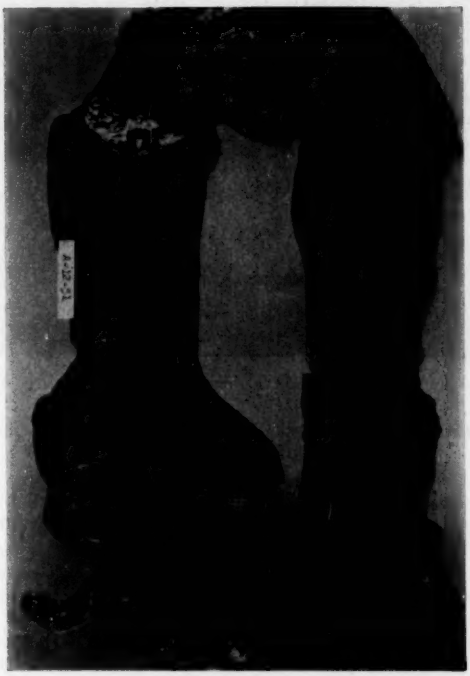

FIG. 3. Gross specimen of colon showing multiple tiny ulcerations from ileocecal valve to midportion of rectum, ulcerations averaging approximately 0.2 cm. in greatest diameter.

whole blood transfusions and plasma. However, in spite of the initial improvement of the child, abdominal distension slowly increased. The colostomy opening was constantly irrigated and was felt to be draining well. On the 4th postoperative day, the infant was doing better. The abdomen was now soft and the colostomy was closed. The infant was placed on an evaporated milk formula.

On the 10th postoperative day, the symptoms of abdominal distension, vomiting and paucity of stools recurred. A WBC revealed 29,000/cmm. with a differential of 78% neutrophiles, 20 lymphocytes and 2 monocytes.

On the 19th postoperative day, due to persistence of symptoms and gradual decline of the infant's condition, a transverse colostomy, with lysis of the intestinal adhesions was performed. At this second exposure, the small intestine was found to be dilated and adherent to its own loops and to the anterior peritoneal wall by plastic fibrinous adhesions. The large intestine was dilated down to the rectum and adhesions here were also freed. Following this second operation, the infant steadily improved on a skimmed lactic acid milk formula and banana. Small formed soft stools were obtained through the colostomy opening. The infant was discharged on the 81st hospital day.

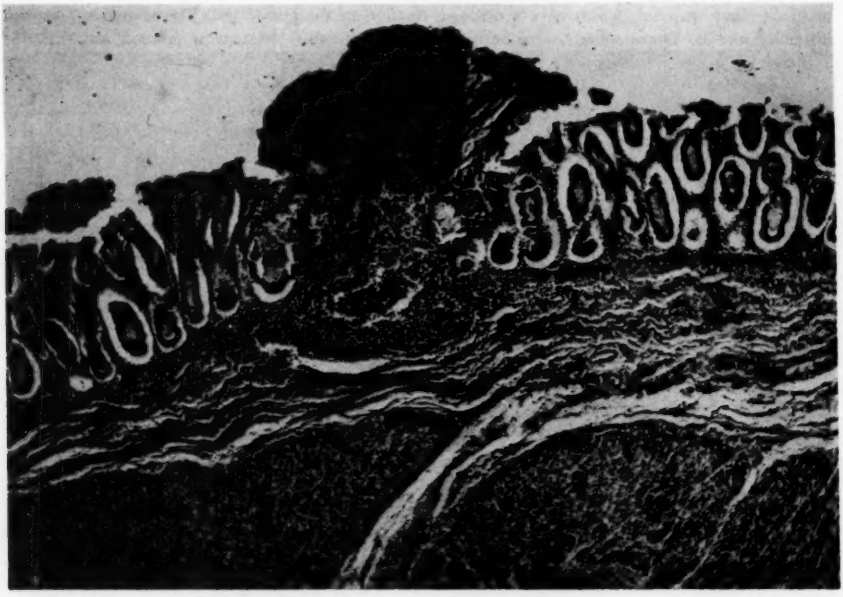

FIG. 4. Photomicrograph of section of colon showing typical ulcer with exudate.

The infant was readmitted to University Hospital at the age of 8 mo. for closure of the transverse colostomy.

Admission physical examination revealed a well developed infant, now weighing 9.1 kg. The only positive physical finding was a colostomy opening on the abdominal wall.

On the 12th hospital day, a closure of the transverse colostomy was performed. The infant did well after the operation and was taking feedings by mouth. On the 8th postoperative day, gradual abdominal distension developed and the temperature rose to 39.4°C. The infant then developed a diarrhea and had 5 large loose to watery brown stools within 12 hr. In addition, the infant began to vomit his feedings.

Oral feedings were discontinued and parenteral feedings started. In spite of adequate intravenous fluids and electrolytes, as well as antimicrobial agents, the infant's condition grew steadily worse.

A scout film of the abdomen at this time revealed dilated loops of transverse colon on the right side with gas in the descending and sigmoid colon.

In spite of all efforts at supportive therapy, the infant died on the 23rd hospital day.

Pathology: Only the pertinent pathologic findings are outlined.

Alimentary Tract: Esophagus: Measures 11.0 × 1.5 cm. The mucosa has a greyish-white appearance and its surface is covered by small flecks of a blackish-brown material. Stomach: Measures 20 cm. along the greater curvature, 8 cm. along the lesser curvature and 10 cm. in maximal fundal circumference. The rugal pattern is maintained and the mucosa is covered by a mucoid material which is generally clear but contains some areas of dark reddish-black material. The pylorus is patent. The duodenum does not appear unusual. The jejunum is not remarkable but the most of the ileum shows marked congestion of the serosal vessels with some thickening of the wall and greenish-yellow patchy diphtheroid membrane on the mucosal aspect. The appendix is present and measures 3 cm. in length and 0.8 cm. in diameter. It is bound down to the retrocecal portion.

On opening the large intestine one is struck by the sudden transition in the appearance of the mucosa (see Figs. 3 and 4). The entire mucosa from the area of ileo-cecal valve to the midportion of the rectum shows a sprinkling of tiny islands of ulceration averaging approximately 0.2 cm. in greatest diameter. These islands are stained light yellow. Between the islands the mucosal surface

is pale and smooth and there are numerous punctate areas of the mucosa which show a dark reddish or blackish-brown appearance. These areas average approximately 0.4 to 5 cm. in size. In the midportion of the transverse colon, there is an indurated area containing numerous suture materials. Apparently this area represents the end-to-end anastomosis following the transverse colostomy. There is no evidence of leakage at this point nor is there evidence of abscess along the entire bowel. Distal to the midpoint of the rectum the mucosa does not appear unusual. No strictures nor valvelike obstructive areas are observed in any other portion of the bowel. The wall of the large intestine averages 0.4 cm. in thickness. Cultures from the intestine at postmortem were negative for enteric pathogens.

Microscopic examination revealed:

Ileum: These sections are from areas grossly covered with a friable yellowish-grey membrane. The membrane is seen to be composed of a layer of fibrin in which are enmeshed innumerable polymorphonuclear leukocytes and lymphocytes overlying a congested and somewhat fragmented mucosa which also shows infiltration by inflammatory cells and what appear to be myelocytes. The submucosa is also infiltrated by these cells. The muscularis does not appear unusual but the serosa is thickened and infiltrated by polymorphonuclear leukocytes, lymphocytes and plasma cells. Some areas of the mucosa show a simplified epithelium which suggests regeneration.

Large Intestine: Multiple sections of large intestine taken from the grossly involved areas show the mucosa to be generally intact. However, there are scattered areas which show necrosis and ulceration of the mucosa characterized by the appearance of small areas of fibrin containing numerous polymorphonuclear leukocytes, red blood cells and nuclear dust which replace the mucosal elements. Many of these areas are seen overlying hyperplastic lymph follicles in the submucosa. Between these ulcerated areas the mucosa does not appear altered. The submucosa in some of the sections shows edema and thickening while the muscularis mucosa is clearly demarcated. The muscularis and serosa generally show no unusual features. Meissner's and Auerback's plexuses show no changes of interest. Stains for bacteria reveal gram-negative rods on the superficial portions of the exudate but not in the bowel wall. Section of rectosigmoid junction shows a transitional thickening of the submucosa by edema fluid in the sigmoid area.

Final Diagnosis: 1. Acute ulcerative colitis; 2. Acute ileitis.

Conclusion

A case of ulcerative colitis in the newborn infant is presented with roentgenographic and postmortem data. This is the earliest case on record with roentgenographic studies of the colon, the latter being made at 24 days of age.

References

1. Jackman, R., Bergen, A. J., and Helmholz, H., Life histories of 95 children with chronic ulcerative colitis, Am. J. Dis. Child. **59**:459, 1940.
2. Hart, J. A., Ulcerative colitis with perforation in newborn, Texas State J. Med. **42**:286, 1946-47.

Spanish Abstract

Colitis Cronica Ulcerosa; Un caso en un recíen nacido

Solamente existen tres casos de colitis de este tipo en la literatura médica iniciados en el primer año de la vida y uno en un recíen nacido que a la autopsia mostró ser una colitis ulcerosa crónica perforada.

El de estos autores es el primero en que se hace un estudio radiológico completo.

Se trata de un niño de 21 días de edad admitido en el hospital con el síntoma principal de vómitos que se iniciaron tres días después del nacimiento simultáneamente con constipación. En una ocasión la evacuación tuvo una pequeña cantidad de sangre. El vómito fué intermitente, nunca en proyectil y se controlaba con antiespasmódicos. Dos días antes de admitirse se presentó concomitantemente distensión abdominal. Al examen físico solo se encontró algo de fiebre, disminución de peso y distensión abdominal con ligera circulación venosa colateral del abdomen. Los análisis clínicos revelaron ligera anemia y varios coprocultivos fueron negativos; los rayos X

demostraran distensión moderada de los intestinos y ulceraciones e irregularidades múltiples de la mucosa del colon que era de aspecto tubular en toda su extensión y sin pliegues. La impresión radiológica fué de colitis ulcerosa. Pensándose en una oclusión intestinal se hizo laparotomía pero el diagnóstico no fué comprobado encontrándose engrosamiento de las paredes del íleo, ciego, colon ascendente y parte del transverso el cual estaba muy friable y considerablemente inflamado, practicándose una colostomía del colon ascendente. Debido a la recidiba de los síntomas después de un período transitorio de mejoría se realizó posteriormente una colostomía transversa a partir de la cual hubo mejoría franca, y el enfermo se envió a su domicilio.

A los ocho meses se admitió nuevamente para cerrar la colostomía ya que el niño pesaba alrededor de 9 kgs., pero el postoperatorio se complicó con distensión abdominal, temperatura y diarrea profusa terminando con la vida del paciente en las próximas dos semanas. El estudio postmortem reportó fundamentalmente numerosas ulceraciones diminutas en todo el colon que microscópicamente correspondían a áreas diseminadas de necrosis y ulceración de la mucosa cubiertas de fibrina e infiltradas con gran número de leucocitos polimorfonucleares y eritrocitos. Muchas de estas áreas de fibrina se encontraban cubriendo folículos linfáticos hiperplásticos de la submucosa. El yeyuno presentaba zonas cubiertas de una membrana difteroide verde amarillenta y algo de engrosamiento parietal, membrana que estaba constituida por una capa de fibrina infiltrada profusamente por polinucleares y linfocitos, infiltración que se extendía a la mucosa, submucosa y serosa, respetanto la muscularis.

121 East 60th Street

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

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Atlanta, Ga.
Died Feb. 1, 1952

Dr. Albert James Bell
3641 Kendall St.
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Died Feb. 24, 1952—EMERITUS

Dr. Robert Alfred Black
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Died Jan. 13, 1952—EMERITUS

Dr. Coursen Baxter Conklin
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Died March 2, 1952

Dr. Clain Fanning Gelston
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Died Nov. 28, 1951—EMERITUS

Dr. Norman L. Hawkins
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Watertown, N.Y.
Died Jan. 31, 1952—EMERITUS

Dr. Thomas F. Humphrey
115 N. Perry St.
Dayton, Ohio
Died May 11, 1951

Dr. George P. Hunt
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Pittsfield, Mass.
Died May 22, 1951—EMERITUS

Dr. J. H. Mason Knox
211 Wendover Road
Baltimore
Died Dec. 31, 1951—EMERITUS

Dr. Andrew J. Thornton
4246 Trias St.
San Diego, Calif.
Died March 3, 1952—EMERITUS

Dr. Samuel Wetchler
303 E. 17th St.
New York City
Died Nov. 26, 1951

Symposium

NEUROLOGICAL CONDITIONS IN CHILDREN

HERBERT H. JASPER, M.D., *Chairman,* Montreal; DONALD MCEACHERN, M.D.,* Montreal, and REUBEN RABINOVITCH, M.D., Montreal; WILLIAM A. HAWKE, M.D., Toronto; DONALD L. MCRAE, M.D., Montreal; WILDER PENFIELD, M.D., Montreal; HERBERT H. JASPER, M.D., Montreal; JAMES PRESTON ROBB, M.D., Montreal, and FRANCIS L. MCNAUGHTON, M.D., Montreal

INTRODUCTION

HERBERT H. JASPER, M.D.

It is indeed with great pleasure that neurologists of Canada have accepted the invitation of the Academy to participate in its meeting in Toronto and we take this occasion to express our sincere welcome to all our colleagues from south of the border.

When Dr. Orr asked me to organize this Symposium, he added that he would like it to be an "all Canadian show." I objected seriously to usurping the program in this manner and not inviting several outstanding speakers from among our colleagues in the United States who would have added greatly to this program. But finally we have yielded to Dr. Orr's persuasiveness in giving you a sample of some of the work being done in this country. We have the good fortune of possessing, in Canada, a Neurological Institute which is rapidly becoming a Canadian National Institute, established in Montreal under the direction of Dr. Wilder Penfield, who is to participate in the Symposium today, speaking on his favourite subject, epilepsy, with particular emphasis on a new conception of focal epilepsy in children. Dr. William Hawke, of the Hospital for Sick Children in Toronto, whom we like to claim as an adopted member of the staff of the Montreal Neurological Institute, will present some of the results of his life long studies of behaviour problems in children. Dr. McEachern, who was unable to attend this meeting because of ill health, has been replaced by Dr. Rabinovitch, who will present a summary of his extensive experience in the study of neuromuscular diseases, a subject which presents puzzling problems to most pediatricians.

Following Dr. Penfield's presentation of a neurosurgical approach to epilepsy in children, I shall try to present a somewhat different point of view concerning the use of electroencephalography in the diagnosis and management of epileptic patients and Drs. McNaughton and Robb will give us their experience in the medical management of epilepsy.

We sincerely hope that you may gain something of interest and value to pediatric neurology from the experience of your Canadian colleagues who are to participate in this Symposium.

NEUROMUSCULAR DISORDERS OF CHILDHOOD†

DONALD MCEACHERN, M.D.,* AND REUBEN RABINOVITCH, M.D.

Disorders of muscular function which may make their first appearance in infancy or in childhood include conditions which affect the anterior horn cell, the nerve fibre, the neuromyal junction or muscle fibre.

Congenital myotonia in newborn infants manifests itself in suckling difficulties, Graefe's sign, and protracted contraction of the orbicularis oculi when washing the face with cold water. The involuntarily protracted muscular contraction following voluntary, mechanical or electric stimulation persists after nerve block, indicating a peripheral mechanism. Myotonic muscle is abnormally sensitive to potassium, and epinephrine reduces myotonia in goats and in humans. Desoxycorticosterone

Presented at the Annual Meeting of the American Academy of Pediatrics, Toronto, Oct. 23, 1951.

* Deceased.

† Based on material presented in an original article published in Advances in Internal Medicine, Chicago, The Year Book Publishers, Inc., 1950, vol. 4, pp. 201-262.

abolishes myotonia in the goat. The curarizing action of quinine diminishes neuronal impulses reaching the muscle fibre and produces clinical improvement. Cortisone abolishes the abnormal contraction.

Myasthenia gravis can occur in the newborn and should always be considered when gross muscular weakness or inability to suck is noted. Differential diagnosis should include amyotonia congenita and cerebral birth injury. The possibility that the thymus elaborates a curare-like substance which acts as a barrier at the neuromyal junction is worth investigating, as are modifications in myasthenic symptoms noted during pregnancy or with change in thyroid function.

The hereditary progressive muscular dystrophies detected at the walking age appear to be improved by prolonged daily intake of wheat germ oil concentrate in doses averaging 60 mg. alpha-tocopherol. Creatinuria, indicating a marked degree of breakdown of muscle tissue, is the most characteristic biochemical finding. The difficulty in establishing a human counterpart to the neuromuscular disorder seen in animals with vitamin E deficiency may be due to faulty digestion or absorption of the vitamin in children suffering from a dystrophy. Thus, vitamin E is relatively ineffectual when given parenterally to animals with nutritional muscular dystrophy, but recovery occurs when this vitamin is given by mouth, indicating that it is conjugated or changed in some way during digestion to form the antidystrophic principle. There is regrettable confusion in clinical reports as to whether pure alpha-tocopherol, mixed tocopherols, whole wheat germ, wheat germ oil or one of its fractions has been used.

Familial periodic paralysis may appear in infants. It can be detected by low serum potassium which appears to be due to a fault of potassium metabolism. Rapid improvement occurs following adequate intake of this salt. Attacks can be provoked by administration of epinephrine, glucose or adrenal cortical extract, suggesting involvement of the carbohydrate cycle. The T-wave change in the ECG is also a rapid test for changes in serum potassium level.

ORGANIC FACTORS IN BEHAVIOUR DISORDERS

WILLIAM A. HAWKE, M.D. (Toronto), M.R.C.P. (London), F.R.C.P. (Canada)

This is a brief discussion of the methods by which organic diseases affect behaviour. To illustrate these methods, one disease, cerebral palsy, is selected because it seems to demonstrate clearly the various mechanisms involved.

In general, organic lesions affect behaviour in three ways: I. Through the direct effect of the organic lesion upon the central nervous system of the individual. II. Through the emotional reaction of the individual to the clinical symptoms produced by the disease. III. Through the emotional reaction of the environment (parents, siblings and community) to the clinical symptoms. These reactions in turn affect the behaviour of the individual with the disease.

I. The direct effects of the organic lesions upon the central nervous system are multiple, but of these 3 are particularly important.

a. The reduction of intelligence by a disturbance of function of the cerebral hemispheres. This may be confused with "pseudo-retardation" produced by the limited environment of these children and the reduction of the normal stimuli for intellectual growth. It may also be confused with specific disabilities of perception, particularly sensory or motor aphasiae, word blindness, alexia, etc.

b. The production of convulsive attacks. These attacks may produce associated mental deterioration, confusion through constant subclinical attacks or through periodic disturbances of behaviour of the psychomotor pattern. In addition to this excessive medication may produce disturbances of behaviour.

c. An organic or physical disturbance of the emotional control of the individual. This is probably due to involvement of the basal ganglia and/or interference with the cortical controls of these areas. It is shown by marked emotional lability and excessive reaction to external situations and stimuli.

II. The emotional reaction of the individual to the clinical symptoms is varied, but includes the following patterns of behaviour. Feelings of

a. Inferiority
b. Frustration
c. Anxiety
d. Dependency

e. Emotional and physical isolation from other individuals.

There are other patterns of behaviour but these are the ones most commonly encountered. The outward reaction of the individual child to these attitudes depends upon the presence or absence in the child of such qualities as aggression, drive and energy. For example, the shy passive child frequently tends to withdraw into a shell away from personal contacts and surrenders to his physical limitations. On the other hand the aggressive child attempts to ignore his limitations and forces himself into close, often undesired, relationships with other individuals. Quite frequently basic feelings of inadequacy and inferiority in these children become overcompensated and appear to the casual observer as attitudes of superiority.

III. The environment of the individual child reacts to the physical symptoms in various ways. For example, the parents frequently show the following reactions:

a. Fatigue, irritability, exhaustion or depression may be produced by the constant physical care of the child and the uncertain prognosis.

b. An intensification of previous difficulties between the parents may be produced by the above factors.

c. Rejection of the child may occur either in open or hidden form. This may occur because of the physical unattractiveness, the presence of mental deficiency, or the gross restrictions imposed upon the parents by the child.

d. Marked anxiety and concern over the welfare of the child may develop and ultimately lead to overprotection of the child with negligible discipline and absent training.

e. Feelings of guilt frequently develop because the parents feel in some way responsible for the condition which has crippled their child.

f. An inability to accept reality is frequently present and evidenced through their inability to accept a factual appraisal of the child or a poor prognosis in terms of ultimate development.

g. Neglect of the normal children in the family may occur because of the time and energy focused upon the handicapped child.

h. A disturbed relationship with the medical profession is frequently seen. The parents blame the physicians for the production of the condition through faulty obstetrics, for erroneous diagnoses in infancy and for their inability to successfully treat the child.

There is frequently an effect upon the siblings of the child. These siblings often have a deep pity for the handicapped child. However, the constant focus of the family upon the paretic child often leads to frank resentment and jealousy. Since these attitudes are unacceptable, the siblings find themselves in constant emotional turmoil with feelings of affection, rejection and guilt at varying times.

The community has always been affected by these children. The adults are often unduly curious or critical of the parents; the children, cruel and mocking. The parents of the handicapped child are particularly aware of these attitudes and often unduly sensitive to them.

These disturbed attitudes of parents, siblings and community will affect the behaviour of the crippled child, frequently increasing previous attitudes and patterns of behaviour. There is often an exaggeration of such attitudes as inferiority, inadequacy, frustration, dependence, isolation, etc.

This article attempts to outline the mechanisms in which organic diseases, in this case cerebral palsy, affect the behaviour of many people, the patient, the parent, the siblings and the community, through various mechanisms, some of which are obvious and easily understood, and some of which are less obvious and less easily understood.

ROENTGENOGRAPHIC FINDINGS IN CEREBRAL LESIONS OF BIRTH AND INFANCY

DONALD L. MCRAE, M.D.

When the brain is growing the cranial vault is thin and develops brain markings. When brain growth ceases the vault thickens and brain markings fade. When intracranial pressure is elevated the sutures are separated and the head enlarges. An approach to the interpretation of skull radiographs in infants and children based on comparison of the width of the cranial sutures with the thickness and texture of the cranial vault is described.

When a cerebral infarct occurs in early life it causes smallness of the ipsilateral cerebral hemisphere

with smallness of that cranial chamber. The underlying lateral ventricle enlarges. When an angioma is present, it may mask some of the signs of atrophy, or even show some signs of a space-occupying lesion. In less severe damage leading to microgyria the normal convolutions may grow over the small ones, pushing them inwards, thus preventing ventricular enlargement. The ipsilateral hemisphere is small. A picture of a small cranial chamber with symmetric lateral ventricles will result.

An approach to pneumoencephalograms based on comparison of symmetry or lack of symmetry of the skull with symmetry or lack of symmetry of the lateral ventricles is described.

The following practical classification of cerebral lesions of birth and infancy is used.

A. Acute Lesions
   Average Head: Expanding lesions
   Traumatic lesions
   Inflammatory lesions
   Developmental abnormalities

B. Chronic Lesions
   Small Head: Microcephaly (small brain)
   Premature closure of sutures
   Average Head: Seizures
   Choreoathetosis
   Diplegia and paraplegia
   Cerebellar ataxias
   Large Head: Subdural hygroma
   Macrocephaly
   Expanding lesions

THE EPILEPSIES OF CHILDHOOD

WILDER PENFIELD, M.D.

The first objective of treatment is obviously to stop the seizures. But when it comes to surgical therapy—the radical ablation of epileptogenic areas of cortex is more easily carried out, and with greater accuracy after the age of 10 years when boys and girls will cooperate and help during craniotomy under local anaesthesia.

It has been our policy in the past, therefore, to wait for the dawn of understanding that comes, as a rule, between 8 and 12 years of age. But at present we are being forced to reconsider the wisdom of this attitude.

There are young children and infants who have received brain injury due to ischaemia or trauma, lesions usually acquired at birth, who develop focal seizures and whose intelligence fails to develop or even disappears upon the advent of the seizures. There are such patients who become increasingly hemiplegic with the continuance of attacks. Every pediatrician of any experience must have seen this sad progression more than once. For lack of better explanation he may assume encephalitis or some un-named degenerative disease of the brain.

There may be another explanation. In the patient who receives a brain insult and who is destined to develop epileptic seizures, there follows a gradual change in injured gray matter that eventually results in seizures years after the lesion was established. That focus of epileptogenic activity may interfere with the function and the evolution of the uninjured portions of the brain if there are any. Local seizures become generalized. Localized electrographic abnormality is succeeded by generalized abnormality.

When such a train of events is established in infancy and the child arrives at years which should be years of understanding there may be little left to save. Thus we have been forced to reconsider our policy in regard to radical ablation of epileptogenic cortex in those cases in which there is evidence of progressive intellectual degeneration or progressive weakness.

In the treatment of epilepsy, periods of 5 to 10 years should be allowed to elapse before summary and conclusion is made of a series of adequate size.

We have in the past made 3 follow-up studies of the results of surgical ablation of focal atrophic epileptogenic lesions of the cortex. The first (which was carried out with Theodore Erickson) included all cases of this type operated upon at the Montreal Neurological Institute between 1929 and 1939 (115 patients).

They were followed from 1 to 11 years. In this series 43% were placed in the success group, which means that each of them either had no postoperative attacks, or had 1 or 2 attacks before cessation.

The second study carried out with Harry Steelman covered the period of 1939 to 1944 (Penfield and Steelman, 1947) with a follow-up period of 1 to 7 years—59 cases of cortical excision with an operative mortality of 1.2%. Of these 55.8% were placed in the success group. That is to say that about half this group had had no attacks after operation and the other half had 2 or 3 attacks before cessation.

The third report carried out in 1950 with Flanagan consisted in a follow-up of 60 cases of radical operation for temporal lobe epilepsy which Gibbs and Lennox call psychomotor. The results were about the same, 55% of undoubted success.

Now these were for the most part adults in each series. But it may be pointed out that of the 59 cases reported in the second series 17 patients were suffering from seizures produced by an unquestioned birth injury. In many other cases birth lesions were a possible cause of the lesions found. The incidence of success as the result of operation rose in these 17 cases from the general average of 56% to 76% success. Thus it may be seen that birth injury provided us with our most favorable group and the attacks usually began in childhood.

ELECTROENCEPHALOGRAPHY

HERBERT H. JASPER, M.D.

You will recall the original description of Gibbs and Lennox of 3 principal types of epileptic seizure, namely, petit mal, grand mal and psychomotor, and that each of these kinds of attack were manifest by characteristic and distinctive forms of electroencephalogram taken during the seizure.

It should be made clear from the beginning that the petit mal form of attack is not just a minor seizure but it is the momentary, sudden loss of consciousness, lasting a few seconds with immediate recovery so commonly seen in children with epilepsy. There is usually no warning, except in rare instances. This type of seizure should not be confused with minor attacks of a different form which are not associated with immediate sudden loss of consciousness and which may be merely minor attacks of focal cortical epilepsy.

During these 3 forms of seizure the characteristic EEGs, namely, the familiar 3/sec. spike-and-dome discharge for petit mal, the rhythmic 4 to 6/sec. activity during the so-called psychomotor seizure and the more rapid multiple spike or rhythmic spike discharge associated with the major convulsion of attack, have received abundant confirmation from hundreds of investigators throughout the world. There has not been such general agreement that all epilepsies can be adequately pigeon-holed into these 3 types. Furthermore, the attempt to diagnose these 3 forms of epilepsy on the basis of the form EEG alone has been often misleading.

In the electroencephalographic examination of the majority of epileptic patients the diagnosis is not made on the basis of an electric discharge occurring during a clinical seizure, but it is made on the basis of the form and localization of epileptiform waves which occur during intervals between clinical attacks, since the patients do not frequently enough favor us with attacks during the recording of the EEG. On the basis of epileptiform discharges in the EEG an attempt is made to make a diagnosis of the type of epilepsy in any given patient.

In a recent survey of the records from over 2000 epileptic patients carried out with the late Dr. Kershman and myself, it was soon apparent that any form of paroxysmal discharge, including the spike-and-dome, the so-called psychomotor patterns and so forth, could be derived from a focal cortical epileptogenic lesion and that this lesion might be present in most any part of the cortex from the frontal to the occipital or temporal regions. The logical deduction from these facts is that the wave form alone of the EEG is not a reliable index for classification of the epilepsies.

For example, if one finds a spike-and-dome pattern in the EEG and it is localized to, let us say, the postcentral gyrus of one hemisphere, are we to call this petit mal epilepsy because of the characteristic spike-and-dome complex? The patient does not have attacks of sudden loss of consciousness, but on the contrary, he has Jacksonian sensory motor seizures.

It should be obvious that to call these electrographic discharges "petit mal," or even petit mal variant, because they are of the spike-and-dome form, only leads to confusion and mismanagement of the patient. I could cite numerous other examples, especially of the so-called "psychomotor"

electroencephalographic pattern being recorded from focal areas of the cortex in the parietal or frontal region and not associated with any seizures which, by the greatest stretch of the imagination, could be classified as psychomotor in type. When this form of electroencephalographic abnormality is localized to the temporal region, it may be related to psychomotor attacks, but even then we find this true in about one half of patients with temporal lobe seizures.

With regard to grand mal, we have also found rapid multiple spike discharge from a focal cortical epileptogenic lesion even present during the intervals between attacks. To speak of this as grand mal activity is meaningless for it simply represents the focal cortical epileptiform discharge and the form of the attack itself has no specific relationship to this form of electric discharge but is determined by the functional characteristics of that particular area of cortex in which the focus happens to lie. Regardless of the type of epilepsy, all seizures look alike when they have reached the stage of a major generalized convulsion, so that grand mal in this sense is also of no value for the differentiation of the epilepsies.

For many years we have been trying to discover why there seem to be relatively higher percentage of focal cortical epilepsies in Canada and so few true grand mal epilepsies by comparison with statistics from various laboratories in the United States. It is only recently, in discussing this with workers in the States, that we have discovered that it is the tendency in many laboratories to classify a patient as grand mal if he has major convulsive seizures, regardless of their manner of onset. It soon became apparent that a large proportion of the patients classified as grand mal in many laboratories were actually patients with focal cortical seizures, which proceeded into major convulsions. Without a careful analysis of the seizure pattern and extremely detailed localization studies in the EEG, the focus of onset may not be detected. This is largely because of a general lack of appreciation for the extremely varied forms that epileptic seizures may take, depending upon their cortical focus of onset, as described in the previous paper by Dr. Penfield. It is necessary, therefore, that we reorganize our thinking regarding the use of the EEG in our understanding and management of the convulsive disorders, if the use is not to become abuse and the management is not to become mismanagement.

The possibility of the misuse of electroencephalography is enhanced by the fact that it is an attractive and somewhat mysterious laboratory technic to most pediatricians, not having received basic training in electronics and electrophysiology. This is enhanced by the general trend towards mechanized medicine and specialization, which I presume applies to pediatricians as it does to other branches of the medical profession today. It is much easier for the pediatrician to order an EEG in the hopes of having it provide him with the correct analysis or diagnosis of a child with seizures than it is for him to take the trouble of carefully analyzing the history and pattern of the attack from the onset in an attempt to derive a conclusion on the basis of clinical evidence.

The EEG cannot be used to give an automatic nickel-in-the-slot diagnosis of epilepsy. In fact it may be misleading as often as helpful unless carefully correlated with other clinical observations. Perhaps it is now time that we had a general reconsideration of how best we can use the data furnished by the EEG in handling the convulsive disorders.

In the first place it seems well to abandon the conception that seizures of any particular form can be identified with any particular form or frequency of the EEG. A spike-and-wave is not equivalent to petit mal, nor is any other form of discharge equivalent to a form of seizure. The brain cannot be considered a homogeneous organ like the spleen for example which produces one form of attack when it beats slowly at 3/sec., for example, and another form of attack when it beats more rapidly.

The statement that "the brain acts as a whole" is a sterile notion for, from the preceding paper of Dr. Penfield, it is obvious that it is composed of a variety of interrelated parts with distinct functions which manifest themselves in different forms of seizure. Our first problem, therefore, in the analysis of any epileptic patient is to try to understand what part or what system in the brain is primarily involved in the onset of the seizure, just as in any other form of clinical diagnosis the first step is the attempt to locate the site of the disorder, before treatment can be intelligently applied or pathology understood.

When the brain as a whole seems involved we must decide whether this is a result of infectious or toxic disease—past or present anoxia or ischemia of birth—or a reaction to systemic disease of liver—endocrines, etc. Most important is to determine whether the generalized affection may not be a result of seizures, which may have been initially of focal cortical origin.

ETIOLOGY AND MEDICAL MANAGEMENT OF EPILEPSY IN CHILDREN

PRESTON ROBB, M.D., AND FRANCIS MCNAUGHTON, M.D.

There are many factors which give a tendency towards epilepsy, factors which lower the threshold sufficiently for the patient to have seizures. These factors may be: hereditary, metabolic, infectious, traumatic, or even emotional.

What actually happens at the site of origin of a seizure is not known. We do know that these factors, acting on the site of origin, lower the threshold and render the brain more susceptible to abnormal electric discharges. Fortunately, also, we have things that raise this threshold.

Hughlings Jackson divided chronic convulsions into 2 classes. (1) "Those in which the spasm affects both sides of the body almost contemporaneously—these cases are usually called epileptic, and sometimes 'genuine' or idiopathic epilepsy. (2) Those in which the fit begins by deliberate spasm on one side of the body, and in which parts of the body are affected one after the other."

As we learn more and more about the various wave patterns as seen in the EEG, and their site of origin within the central nervous system, the distinction between "focal" and "generalized" becomes somewhat artificial. We find increasing evidence of "focal" mechanisms acting even in the case of widespread disorders. The day may come when all epilepsy will be understood in terms of anatomic-physiologic systems within the brain, and a term such as "diffuse" or "generalized" will be obsolete.

One year ago we set out to review the causes of focal epilepsy in children. We both had many fixed ideas, and we endeavoured to adjust these by a study of 100 children with focal seizures from the clinics and wards of the Children's Memorial Hospital and the Montreal Neurological Institute. Only patients in whom the seizures had started before the age of 10 years were considered. There were 65 patients from the Children's Memorial Hospital, and 35 from the Montreal Neurological Institute. All the EEGs were done in the Montreal Neurological Institute and were interpreted by different men under the supervision of Dr. Jasper. Pneumoencephalograms were done in both hospitals. There was a certain amount of overlap. That is, one patient might have attended both clinics, or have been in one or both hospitals. Ninety-three of the patients had had one or more EEGs. The rest were not done for various reasons. It may have been that it was felt they would not cooperate, that we did not feel it would help the patient, or maybe the patient might not have appeared for the test.

Cases were selected that showed one or more of the following features:

1. First, a definitely focal seizure.

2. Secondly, a focal electroencephalographic abnormality even if the description of the seizure could not be classed as focal.

All the patients fell into one or the other, or both of these groups.

3. A third criterion, evidence of cerebral damage, but all these patients fell into one or both of the first 2 groups. There was felt to be evidence of cerebral damage, if there were:

a. Abnormal neurologic signs.

b. Grossly abnormal psychometric evaluation in the presence of normal siblings and normal parents, or

c. Abnormal pneumoencephalogram.

As well as an electroencephalographic localization, an attempt was made to localize the lesion either from the description of the seizure, or from the abnormal neurologic findings. In these patients, we charted all the available data. In many, the patients or their parents were called in to get additional information, and a more accurate description of the seizure and of the etiology was obtained. Frequently, either because the seizures had been infrequent or nocturnal, we were unable to get a good description. These had to be considered as nonfocal seizures, even though the EEG suggested a sharply localized focus.

In some of the younger children they were described as running to their parents as if they were afraid of something. Then, as they grew older, they were able to describe a definite aura. Presumably, they had an aura before, but could only express it as fear.

Focal seizures in infancy and childhood are most readily recognised when motor in type—including such features as head and eye turning, classic movements of face, arm and leg, either simultaneously or by a "Jacksonian March." Often the entire seizure takes place without loss of consciousness. Some-

times it is a postseizure hemiparesis, lasting hours or days, which will draw the attention of parent and doctor to the focal character of the attack.

Sensory phenomena—such as a visual or an auditory "aura"—paraesthesias, vertigo, etc., will only be recognised in older children: also, such focal defects as postseizure aphasia.

Automatism—as a focal manifestation either during or following the seizure—has been uneommon in the childhood group we have observed.

We feel that focal manifestations are often missed through not taking adequate history from the parents, or through inadequate observation and recording of attacks occurring in the hospital or admitting office. Sometimes it is focal findings in the EEG which drive one back to complete the clinical history and confirm the diagnosis of focal epilepsy.

Precipitating Factors: We felt that more time should be spent in trying to determine what the precipitating factors were, but found that our own records were inadequate. There was a fairly large number whose seizures were either nocturnal or occurred in the early morning. In a large number, no reference was made to this, and we did not feel that the figures were of any value.

Such things as etiology, other neurologic disabilities, family history, skull roentgenograms, pneumoencephalograms, intelligence evaluation and social history, and the results of medication were reviewed.

Results: Our figures did not vary a great deal from those of others. Thirty-four could be attributed to difficulty at the time of birth. In 12 there was a definite history of anoxia at birth. In 10 there was a definite history of trauma, such as forceps marks, and 11 gave a history of a difficult birth.

Nine were considered to be due to cerebral vascular occlusion.

Eleven gave a definite history of severe head injury, and were considered to be post-traumatic.

Thirteen were due to miscellaneous causes, including meningitis, congenital anomalies, tuberculoma, lead poisoning, arrested communicating hydrocephalus, encephalitis and tuberous sclerosis.

In 34 we were unable to establish a definite cause.

Of the 100 patients, 81 were considered to have had clinically a focal type of seizure.

With regard to cerebral damage, it is interesting and significant that 69 showed evidence of cerebral damage, as shown by abnormal neurologic findings such as hemiplegia, marked mental retardation in the presence of normal parents and siblings, or an abnormal pneumoencephalogram. Uniformly moderately enlarged ventricles were not considered as an abnormality.

Fifty-seven had some recognizable neurologic disorder. Of these, 33 showed evidence of hemiparesis of a varying degree. These figures were the most surprising thing of all, and we did not realise that the incidence of clinically recognizable brain damage would be so high.

Thirty-nine showed definite evidence of mental retardation. However, only 59 had a definite assessment. The rest were more or less normal.

We were surprised at the number of children who were previously classed as "idiopathic epilepsy," and who, on careful analysis, had focal seizures, had a focal electroencephalographic abnormality, and evidence of focal cerebral damage.

In 35 we were unable to establish a definite cause, and yet in 17 of these, there was evidence of cerebral damage. In many of these, the onset of the seizures was associated with a fever, or there was a previous history of a febrile illness.

Bailey and Hass (1937) pointed out the incidence of dural sinus thrombosis in early life in routine autopsies and suggested that the condition was more common than was suspected. Putnam and Alexander showed that the pathologic changes found in encephalitis, associated with infectious diseases, may have their origin in multiple small thrombi scattered throughout the brain. O'Brien has recently stressed the importance of cortical venousthrombosis. It is our impression that vascular occlusions probably play a large part in the etiology of focal seizures, but we have no way of proving it.

A good deal of the allotted time has been spent on a discussion of the etiology. Perhaps from an academic point of view this is the most interesting, but the patient is not interested in this. He wants to know how to get rid of his seizures.

The basis of the present-day treatment is drug therapy. It is true that one has to consider the whole picture. To have an accurate diagnosis, an EEG, and to know the social background of the patient are all part of the treatment, but still we must turn to drugs to control the attacks.

Dr. William Lennox recently laid down certain principles which bear consideration:

1. Treat the patient—not just his seizure symptoms.

2. Fit the treatment to the fit.
3. Dosage must be individualized.
4. Dosage must be adequate.
5. Persistent trial is essential.
6. Confidence and cooperation of the patient is essential.

For the purpose of treatment, seizures may be divided into 4 simple groups.

1. Generalized convulsions and focal seizures.
2. Petit mal convulsions.
3. Combined petit mal and grand mal.
4. Psychomotor seizures.

In children one usually starts the treatment with phenobarbital for all types. This is simple, safe and effective.

Generalized Convulsions and Focal Seizures: Start with phenobarbital. If this fails, add dilantin®. If this fails, try mesantoin® and phenobarbital—or any combination of these. Occasionally mebaral® may be substituted for phenobarbital. On rare occasions, phenurone® or thiantoin® may be tried.

Petit Mal: Here again, one starts with phenobarbital. If this fails, then add or switch to tridione®. This is frequently miraculous. If the photophobia bothers the child, paradione® may be used.

Combined Petit Mal and Grand Mal: Again start with phenobarbital and add dilantin® and/or tridione®.

Psychomotor Seizures: A psychomotor seizure is best treated like a grand mal attack.

In spite of these medications, patients still have seizures. It is our feeling that seizures secondary to vascular lesions may be resistant to treatment, and then slowly come under control, and will be easily controlled.

Although we emphasise the importance of drug therapy, in closing, I would emphasise the importance of treating the patient as a whole.

Round Table Discussion

EARLY DIAGNOSIS AND TREATMENT OF TUBERCULOSIS IN CHILDREN

EDITH M. LINCOLN, M.D., New York City, *Chairman*
J. B. SCRIVER, M.D., Montreal, and A. D. BIGGS, M.D., Chicago,
Secretaries

Chairman Lincoln: We will try to stay as close to the subject matter as possible and then if we have time and you want to go off into other subjects connected with tuberculosis, we can. I think there is plenty of material for discussion in early diagnosis and the treatment of the early phases of tuberculosis, that is, primary and postprimary tuberculosis. This will take up our time without going into the discussion of chronic pulmonary tuberculosis, since that is not a form of tuberculosis which is common in children.

Specific therapy has changed the attitude of pediatricians to tuberculosis. Formerly a pediatrician took the attitude that the great majority of children who had primary infection, evidenced by positive tuberculin tests without or with positive x-rays, would get better without ever having any symptoms; that a few of them might develop complications such as tuberculosis of the cervical nodes, or of the bones or joints, which could be turned over to a specialist and not be seen again by the pediatrician. A few cases would develop fatal complications such as meningitis or miliary and promptly die. Therefore, there was little of interest to the clinician in the story of tuberculosis in the child. As recently as 5 years ago, just before chemotherapy, I talked to pediatricians in many teaching centers and I was repeatedly told that the diagnosis and the care of tuberculous children was a minor problem and that tuberculosis was practically never seen in their services.

Since chemotherapy there has been a new interest in tuberculosis and I think this is shown partly by this round table discussion. It is also shown by the increasing reports in the literature as you will note if you look over the pediatric journals of the last few years and see the unprecedented number of papers about tuberculosis. Great interest has been shown by phthisiologists as well as by pediatricians in the treatment of tuberculosis in children.

If we are going to treat tuberculosis and to control it intelligently in any community we ought to know what the extent of the problem is. In the early days of the tuberculin test we had many surveys: we know that 95% of the children were infected in Vienna; then surveys were made in St. Louis, Philadelphia and other cities and everywhere we found a high percentage of children infected with tubercle bacilli.

We know that today fewer children are infected but there are very few surveys that tell us exactly how many children have positive tuberculin tests. There are a few reports from hospital groups; we reported on our group in 1938 and showed that while there had been relatively little change in the total number of positive tuberculin tests seen at Bellevue there was a change in distribution and many fewer infants showed positive tuberculin reactions. Dr. Beaven has recently reported on a tuberculin survey of Rochester, N.Y., and has emphasized the reduction in the number of children with positive tests. In most communities, however, we have very little information about the extent of this problem; it is really up to us as pediatricians to find out how much tuberculous infection exists in the children of any community. We know that tuberculosis is a contagious disease and we know that the amount of tuberculosis in the adult population is bound to be reflected in the number of infected children. In rural areas and in moderate sized cities with relatively good housing where conditions of employment are good and where there is a low rate of tuberculosis in adults we expect and find a low rate of tuberculosis in the children and a low death rate. On the other hand, children who live in crowded sections of large cities where the rate of tuberculosis is high have more tuberculosis and a much higher death rate.

I would like to review briefly what has happened over the course of years as far as tuberculosis is concerned. Back in 1900 tuberculosis was a grave problem, although we didn't do much about

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it; there was very little that we could do. In the years since 1900 there has been a steady fall in the number of cases of tuberculosis in the various age groups and again this decline was much more marked in the infants than in the older age groups. The last year for which I have full census figures is 1948 and I picked Minneapolis, in contrast to New York, because we all know there is an excellent tuberculosis service in Minneapolis and they are rightly proud of the low tuberculosis death rate in children. The death rate per 100,000 for all ages is much smaller in Minneapolis than it is in New York City and the different is even greater at the beginning of 1948 than it was in 1940. This is reflected in the number of deaths from tuberculous meningitis. From 1934 to 1944 there are very few deaths from tuberculous meningitis in Minneapolis and even more in New York City than would be expected from the difference in size of population. As I have said before, the real extent of the problem as far as your own communities are concerned is something that you have to find out for yourselves, but there is always a definite relation as we see here between the amount of tuberculosis reported in any community, the number of tuberculosis deaths and the incidence of infection in children. Of course, there are tremendous variations due to differences in economic level and degree of infection. Nevertheless, the pattern of the disease remains exactly the same. That individual child who died of tuberculous meningitis in Minneapolis had exactly the same disease with the same prognosis as the children who died in New York. The difference between Minneapolis and New York is in the number of cases and in the degree of infection leading to variations in course and prognosis. Once fatal complications have developed the pattern is exactly the same.

Now, we shall go on to a discussion of early diagnosis which is an important subject for pediatricians. Diagnosis of any form of primary tuberculosis, as we know, is usually made by case finding methods.

It is made by a history of contact with a case of tuberculosis or by a tuberculin test. The test is done as part of a routine examination, in school, in hospitals or in the physician's office. When tuberculosis is diagnosed by signs or symptoms, the disease is already established and you are not making an early diagnosis.

The early recognition of tuberculosis in any child is important because the most serious complications, miliary and meningitis, are most likely to occur in the first 3 months of the infection. Early diagnosis of these infections will obviously be made most often if you already know that the child has a tuberculous infection and are alerted to the possibility of tuberculous complications. The pediatrician, therefore, is the one who can help most in the early diagnosis of tuberculosis by doing tuberculin tests as part of his regular yearly examinations, and more frequently when he has knowledge of a possible contact with a patient who has tuberculosis. By doing tuberculin tests the pediatrician will not only learn the prevalence of infection in his own group of patients but he will train himself to think of tuberculosis in differential diagnosis.

Diagnosis is obviously the first step toward treatment. In our own clinic we have always felt that every child with primary tuberculosis, or every child with a recent conversion of a tuberculin test, should be treated by increased rest, by a diet high in fat and protein and by extra vitamins even if he is asymptomatic. The contact history and the economic condition of the family also have to be taken into consideration in deciding whether you are going to treat the child in this conservative manner in his own home or whether he has to be sent to a hospital. The degree and duration of conservative treatment depends on an estimate of prognosis. This, in turn, is based on 3 factors: the apparent duration of the disease, the age of the child and the extent of the lesion on x-ray.

The duration of the tuberculous lesion is an important factor in prognosis. We base this opinion on a study that we did between 1930 and 1940. We followed all consecutive cases of primary pulmonary tuberculosis that we saw during this 10 year period. During this period we had 622 cases of primary pulmonary tuberculosis. We found that 90% of the deaths occurred within a year of the first diagnosis; about 75% of the deaths occurred in the first 6 months after the original diagnosis and almost 60% within the first 3 months. That is why we think it is so important to follow and treat conservatively every child who has a recent primary infection whether or not you see it on x-ray. The age of the child is also important in estimating prognosis. In this same group of children the death rate was highest in the group under the age of 6 months and lowest during the so-called safe period between 4 and 9 years of age. The influence of the size of the primary complex on prognosis is harder to determine. However, an attempt was made in our series of cases to measure the primary on x-rays and we found that the mortality rate in the children with the largest lesions was more than double the rate in children with small primaries.

We think we ought to treat conservatively all cases of primary tuberculosis. How are we going to pick the children who need chemotherapy in addition to conservative therapy? The selection of cases always has to be on an individual basis, but by and large you have to depend again on a knowledge of the course and prognosis of the form of tuberculosis under consideration. In order to know what to treat we studied our statistics regarding prognosis. We knew that before chemotherapy 95% of the deaths in our group of tuberculous children were due either to tuberculous meningitis, to various forms of hematogenous tuberculosis or to local progression of the primary with cavitation and bronchogenic spread. Therefore, we decided that chemotherapy would be mandatory in these complications of tuberculosis which constitute about 20% of our ward population. Aside from these forms every case should be considered individually and streptomycin should not be used except for forms of tuberculosis in which it has been proved to be superior to conservative methods of treatment. This rule would restrict the use of streptomycin, in addition to its use for the complications already covered, to forms of tuberculosis which have been shown to yield rapidly to short courses of treatment, for example, tuberculous laryngitis and draining cutaneous sinuses; streptomycin would also be used to "cover" surgical procedures which would be dangerous or impossible without it.

Treatment may also be tried as an elective measure in other forms of tuberculosis such as endobronchial disease and tuberculosis of the bones or nodes. Criteria for treatment in this group will change as results of therapy are evaluated. For instance after treating 30 children with endobronchial disease with streptomycin, we could find no evidence of definite response to therapy and therefore discontinued routine chemotherapy of tuberculous endobronchitis. Follow-up of months or years will sometimes be required before final judgment can be passed on the value of chemotherapy in some complications such as tuberculosis of the cervical nodes.

In addition to the group of cases where chemotherapy is always indicated and the cases for whom chemotherapy is an elective procedure, there is a third group consisting of cases of primary tuberculosis in which we believe the use of chemotherapy is contraindicated regardless of the size of the lesion or the age of the child. At Bellevue this group represents 70% of our ward population. There is no evidence, to my knowledge, that streptomycin hastens the healing of a pulmonary primary. We have all treated children with miliary tuberculosis and tuberculous meningitis. We have seen the miliary melt away under the effect of streptomycin and the meningitis cured and yet the primary pulmonary tuberculosis takes its own course and is still present after the other complications are arrested. There is also no evidence to show that streptomycin will prevent complications. A third reason for withholding the use of streptomycin in uncomplicated cases of primary tuberculosis is the possibility of the emergence of tubercle bacilli, resistant to streptomycin. The occurrence of resistance is diminished with combined therapy, but occasionally resistance develops even when combined therapy is used. Since streptomycin is the only drug we have which will cure meningitis it does not seem fair to use it in nonfatal complications except for short terms of treatment; and certainly not in the very early stage of the disease when meningitis is most likely to develop. Except in short courses streptomycin should be used in combination with another drug. It has been shown definitely that combined therapy enhances the value of the streptomycin, that it delays the emergence of resistance and permits the continuation of bacteriostatic therapy for years. We use promizole® in meningitis, miliary, and more protracted forms of hematogenous tuberculosis. We use PAS in predominantly pulmonary forms such as progressive primaries and of course in chronic pulmonary tuberculosis.

I said before that early diagnosis is important because it leads to the early diagnosis of complications. We are quite sure there is a definite relationship between early diagnosis of complications, which in turn leads to early treatment, and good results of therapy. All over the world the best results are in those groups of patients which have been treated early in the course of their disease. The British have contrasted the good results of treatment of early cases of meningitis with the poor results obtained after late diagnosis. Similar statements have been made by writers from other countries. All the evidence shows that early diagnosis and early treatment leads to the highest percentage of cures.

It is obvious then that the diagnosis of tuberculous meningitis should be made by the pediatrician because he is the one who should be following the child with primary infection who is most likely to develop meningitis. Treatment of meningitis also belongs in the field of pediatrics.

A study of symptoms of onset of meningitis was made in a group of 167 cases that we saw at

Bellevue before chemotherapy and of course all of them died. The common symptoms, vomiting, apathy, fever, anorexia, irritability are all those that we associate with almost any acute infection. That is one reason why I think this is a disease for the pediatrician to diagnose. Of course he is going to be more suspicious of the diagnosis if he already knows that his patient has a positive tuberculin test. Some of the symptoms vary with the age of the child. You rarely see a child who complains of headaches under the age of 5. Convulsions are a common early symptom in infants but a rare symptom of onset in the older child.

We treat all our meningitis and miliary cases with combined therapy. This is an outline of what we use and, of course, no scheme is adhered to rigidly. We give children with miliary 1 gm. streptomycin daily for 4 months; we give the meningitis cases 1 gm. daily for 6 months. If the child with miliary develops meningitis we start treating by the intrathecal method at once. We usually begin with 100 mg. daily regardless of the age or the size of the child and we maintain that dose as long as we can. Sometimes we keep it up for a week, sometimes we keep it up for the full course of 40 treatments. If we can't maintain this dosage we reduce to 50 mg. or we give 100 mg. every other day. Even if the character of the spinal fluid improves rapidly we continue intrathecal therapy for a minimum of 40 treatments. If at the conclusion of the usual course the spinal fluid has not returned to normal we continue therapy by the intrathecal route.

I know there is a great deal of argument about the use of intrathecal therapy and I hope you will tell us some of your experiences treating cases with and without intrathecal treatment. I am perfectly sure that one can treat and cure some cases of tuberculous meningitis with intramuscular therapy alone. But I don't know how to pick out the cases that will be cured with intramuscular therapy. The percentage of cures in series of cases treated with both intramuscular and intrathecal therapy is far greater than in series treated with only intramuscular therapy.

We give promizole® orally starting with a half gram divided into 4 doses every 6 hours until we get a blood level of 1 to 3 mg./100 cc. The range of the dosage is very great as I will show you in a minute and promizole® cannot be given successfully and certainly not without toxicity unless it is controlled by a blood level. We continued promizole® in our first 25 cases for 3 years and we are continuing it in our next 25 cases for 2 years. That period is purely arbitrary of course; we wanted to obtain bacteriostatic action for a long period of time in the hope of preventing later relapse. We had shown that we could cure patients with miliary tuberculosis with promizole® and that they would stay cured. Our original group of 5 patients with miliary that were treated in 1944 are still alive and well and none has ever developed meningitis. So we knew that you could give promizole® safely over a long period of time. Other people use PAS in combination with streptomycin; it has been proved that PAS delays the emergence of resistance and this has not been proved with promizole®. However, clinically we have had no resistance develop in the spinal fluids of cases except as a terminal event. Moreover, those of you who use PAS know that it is often a difficult drug to administer. To give it to a child for 2 or 3 years would be a problem whereas promizole® is an easy drug to administer. Deafness is unfortunately something that occurs in a certain percentage of the children and why it selects some children we don't know. In the last year we have been having an increasing number of cases of deafness. However, we have never had any deafness in children who have been treated with intramuscular streptomycin for other forms of tuberculosis. All the deafness has been in patients treated for meningitis and, therefore, with intrathecal streptomycin. We have always known that patients with pneumococcic meningitis had a certain percentage of deafness but previously patients with tuberculous meningitis didn't recover so we don't know whether the deafness is due in part to meningitis or mainly to the streptomycin. The reactions to intrathecal streptomycin are much more striking than to intramuscular streptomycin. With increased ataxia and vomiting, we keep right on with intrathecal therapy because we think it is important to treat the child regularly in the first weeks of the disease. However, if the child has a high fever, as they sometimes do—40.5° or 41.0°C.—or if he has a convulsion we do reduce the dose or increase the interval between the doses. Sometimes a streptomycin reaction is seen which is more striking than the convulsions and the fever; a reaction in which the child loses all his superficial reflexes, becomes lethargic and may have marked slowing of respirations. After this type of reaction we always reduce the amount of streptomycin given intrathecally. With promizole® we almost always get a slight cyanosis of the lips and finger nails, in the early stages of the administration; a slight enlargement of the thyroid and an elevation of cholesterol usually appears after about 2 or 3 months. We have a few children in whom there has been a question of liver damage which has

been reversible after the drug was stopped. This occurred mainly in the few children who ran high blood levels on small doses of promizole. Occasionally one sees stimulation of secondary sex characteristics in girls and this is the only toxic reaction which is not reversible when the drug is withdrawn.

Reactions to PAS are ataxia, nausea, vomiting and abdominal pain. They don't always occur, but when they do they are disagreeable, and it is difficult to have older children continue with the treatment once reactions have occurred.

In treating children with tuberculous meningitis, we have learned not to expect too much in the first week. Before therapy it was an acute disease and patients died within an average of 19½ days. The response to therapy is slow and even in the child who is going to do well we often see little change in the first weeks; under therapy neurologic signs may develop and a child may pass progressively from the first to the second and then to the third stage of meningitis and ultimately recover. The good signs such as weight gain, increased appetite and falling temperature are not usually seen until the second month of illness.

If the spinal fluid has not returned to normal at the end of the usual period of therapy treatment may be continued. We keep up intrathecal therapy until the spinal fluid has come to normal by which we mean that the sugar is normal, that the protein is stabilized at or below 100 and that the cells do not show marked variation in numbers.

Once we stop streptomycin therapy we watch the child and continue to do lumbar punctures twice a week at first and then every week for a period of at least 2 months. During this time the child is allowed out of bed for short periods. It is important to keep children quiet and keep them under close observation for at least 1 year after the diagnosis of meningitis.

The sugar returned to normal in about ¾ of our cases while they were still on intrathecal therapy. In the remaining 25%, intrathecal therapy was prolonged beyond the usual period. The protein rarely becomes normal during intrathecal therapy and is still somewhat elevated in about half the cases at the end of intramuscular treatment.

In forms of tuberculosis other than meningitis and miliary we do not give as much streptomycin; we have tried to gauge the amount of streptomycin so that we relatively give more to the small baby than we do to the older child because the prognosis is much worse in the young baby.

Dr. Milton I. Levine, New York City: I tried treating a few cases with streptomycin and with the first case I was quite thrilled in that it seemed to subside considerably quicker; however, that was my first case! After that we found no change at all and again, as Dr. Lincoln has pointed out, in cases where there was a primary which had blown up into miliary tuberculosis under treatment with streptomycin the miliary would disappear but the primary would stay. In a case with cervical adenitis a child came in with a large cervical node and then developed miliary tuberculosis. The child received streptomycin and promizole®. I think all of us who treat children with tuberculosis are impregnated with the fact and are using promizole® with streptomycin. The child recovered from the miliary so he was sent home with promizole 3 gm. a day and after about 2 years the thing blew up again. Apparently the promizole® was inadequate in preventing the growth of the organism in the cervical node.

Chairman Lincoln: Whenever you have an area that is inaccessible to the drugs, and it has been shown that streptomycin is not absorbed well in caseous areas, you will have a progression of the lesion.

Question: Dr. Lincoln, would you say a word about the contagiousness of the primary tuberculosis? In most hospitals they are put under strict precaution.

Chairman Lincoln: Dr. Wallgren, as you know, has shown pretty conclusively that primary tuberculosis is probably not contagious. Nevertheless, the presence of tuberculous children on a pediatric ward creates a compensation problem. After all primary tuberculosis is caused by the same tubercle bacillus which is responsible for tuberculosis in adults. On the other hand, those of you who try to obtain tubercle bacilli out of gastric washings know how difficult it is to obtain positive cultures; and the only reasonable method of transmission of these bacilli would be by cough. I don't really think that in the absence of a cough that you have any right to call primary tuberculosis a contagious disease. However, I feel strongly that one should not send a child with a fresh primary to a home where there is a newborn infant without warning the mother of the possible risk of contact, because I think in this very young age group it may take only one cough or sneeze to infect the baby.

Dr. Levine: Among our best results with tuberculous cervical nodes are cases where we have permitted the nodes to suppurate. The fluid was then aspirated and streptomycin 1.0 gm. reinserted. If in a week the node was again fluctuant, a similar treatment was performed. Usually the size of the node diminished considerably in several weeks and there was no further evidence of activity.

I am in complete agreement with Dr. Lincoln's concept concerning the treatment of complicated tuberculosis. However, I believe I am somewhat more optimistic as regards the child with uncomplicated primary tuberculosis between the ages of 2½ years to 12 years. In our observations during this age period we have found no harm whatever in permitting these children to be ambulatory without restriction as long as they remained afebrile. There was no increase in the number of complications and there was no decrease in the speed of recovery. This is in contrast to the opinion of Dr. Arvid Wallgren, who advises bedrest until the sedimentation time has returned to normal, reporting that he finds an increase in complications when children with primary lesions of tuberculosis were ambulatory.

However, I can't help but feel that there is something different about the response to primary tuberculosis in European children as compared to American children. This opinion is shared by a number of other workers who have made numerous observations in Europe and the United States.

For instance, we see very little erythema nodosum accompanying primary tuberculosis in this country, whereas its occurrence is very frequent in Europe. In my own experience of 22 years I have seen no more than a half dozen cases.

Furthermore, in Europe pleural effusions are not uncommon during the course of the primary complex. In this country they are comparatively rare.

It is difficult to determine the cause of these differences in geographic sections of the world, but it probably accounts for necessity of a much more rigid regimen of treatment as advised by Dr. Wallgren in Sweden.

New Speaker: I have been interested in the primary in St. Luke's hospital in the outpatient department and about 10 years ago decided to conduct a little clinical experiment on primary tuberculosis. We gave a tuberculin test to every child who came into the outpatient section. In the first 2 years we had 460 children whom we tested; exactly ¼ of them had a reaction. Each one of those children, 115, have been studied by me since then: I have kept close track of them and the results are remarkable. Any child who reacts we call a primary. It is our opinion that if you analyze x-rays carefully (and we have one of the best x-ray men in the field in our hospital) you can see some kind of a shadow in almost every primary. Not as soon as you get the reaction—but if you follow it you see a shadow eventually. Perhaps you can't distinguish it from a respiratory infection, whooping cough, etc. We took an x-ray every 3 to 6 months, then every year and then the patients were followed for 10 years. At the same time, we took blood counts, urinalyses, sedimentation rates: we weighed and measured the patients every time they came in. They had to come back every 2 months and then once a year. We compiled our data; those children did not have any significant gains in their blood count, there was no change in their urine analysis and that group as compared with the total group gained at the same rate. They gained in height at the same rate and those that we classified as an ordinary primary had no physical findings. Now the pediatricians have a little different viewpoint. Twenty-five per cent of our children who came to the dispensary had ordinary primary and we wouldn't have known it if we hadn't done the tuberculin test and followed up with x-ray. According to what we think, those children don't need anything but there are a few in that group who have an extraordinary primary or a massive shadow. Those that have massive shadows are the ones who go to the tuberculosis people and when our tuberculosis people are talking about primaries they are talking about the unusual primary that get to them. The ordinary primary is a child who plays and runs about actively with unsuspected tuberculosis; these children don't have to be treated. This is entirely different from the patient Dr. Lincoln is discussing; I would call her type of patient an extraordinary primary. The ordinary primary according to our work and the one which the pediatrician usually sees is entirely an asymptomatic disease and you wouldn't know the child had it if you didn't take the tuberculin test. I hope this doesn't confuse the issue.

Chairman Lincoln: I would like to say that in our own group of children with primary tuberculosis we realize we are dealing with a heavily infected group. Before chemotherapy about 20% of our patients died and we have fortunately been able to continue to follow most of the survivors.

Probably many of our survivors fall into the group of simple primaries to which the last speaker referred but on first observation it is not possible to determine which children are going to do well. Eighty-five per cent of the patients we have on our ward were originally sent in because they were contact cases or were found on our own pediatric wards through the routine use of the tuberculin test.

Dr. John T. Kometani, Honolulu: Of those who recovered from meningitis, what about their mental status?

Chairman Lincoln: The best way to answer that is to say that we never had a child survive whom we regretted treating. We have no so-called "vegetables." We have had children who had behavior difficulties when they recovered but children who have been in bed for 6 or 8 months would very likely have difficulties if they had some other disease. The deaf child is particularly apt to have behavior problems. I am sure, however, that with continued follow-up of our cases that we will find evidence in some children of cerebral damage.

Dr. Cochrane, Toronto: Would you mention the place of (a) intraventricular therapy and (b) old tuberculin in meningitis according to any results you have had?

Chairman Lincoln: Most of the early cases that are treated recover; most of the cases that are diagnosed late and a few of the cases that are diagnosed early don't do well. After a month or more of therapy they are still drowsy or even comatose and they may develop signs of block. Since severe reactions occur in the course of PPD therapy it is essential that burr holes be made before beginning treatment in order to be able to relieve pressure promptly.

Dr. Henry B. Strenge, Oklahoma City: What would you think of the administration of PAS to each child with primary tuberculosis in an effort to avert complications?

Chairman Lincoln: The experience of people who have treated meningitis with streptomycin and PAS is that the combination has as little effect on the primary as streptomycin has, so that I don't think there is any reason to think that it would cure the primary when administered without streptomycin. The same answer holds for prevention of complications.

Dr. Ralph D. Sussman, Burlington, Vt.: What is your opinion as to the value of the patch test?

Chairman Lincoln: I think the patch test is a valuable screening test, but I don't think it should be used as a final answer if you suspect tuberculosis. If any child has been shown to be tuberculin negative to 1 mg. it is sufficient to do a patch test at intervals thereafter to discover tuberculosis. It is extremely important that the doctor know how to read the patch test. The directions state that you must have vesiculation but about twice a year I see a child who has had a patch test interpreted as positive on the basis of swelling and redness without vesiculation, which proves to be negative when tested with a Mantoux through 1 mg. in strength.

Dr. Alfred D. Biggs, Chicago: Should the streptomycin dose be divided?

Chairman Lincoln: We give streptomycin only once a day unless the child is very small and very thin in which case we divide the dose. In many of our cases, exclusive of the miliary and meningitis cases, we are giving streptomycin only twice a week with PAS every day, as this method has been shown to be as effective in adults as daily administration of streptomycin and markedly delays the emergence of organisms resistant to streptomycin.

Dr. Biggs, Chicago: Do you not have occasional cases where it is difficult to tell whether it is a primary or reinfection?

Chairman Lincoln: I presume that you refer to cases in older children or adolescents. Dr. Amberson always says that it doesn't make any difference in this age group whether you have reinfection or primary tuberculosis because you should treat it as reinfection in either case.

Dr. Biggs, Chicago: So they get streptomycin anyway?

Chairman Lincoln: They get conservative therapy for minimal disease and streptomycin for moderately or far advanced tuberculosis.

Dr. Henry C. Thatcher, Auburn, Me.: What is the present consensus of opinion in regard to the treatment of nonsuppurative lymphadenitis with x-ray?

Chairman Lincoln: We believe it is primarily a surgical condition. With x-ray treatment there is the danger of increased fibrosis making ultimate surgery more difficult. It may have a place in therapy but we have not used it for many years.

Dr. Morley P. Welles, Columbia, S.C.: How long do you continue the use of streptomycin in cases other than meningitis?

Chairman Lincoln: It varies with each case. We usually treat with daily streptomycin for 2 to 4 months. In children with progressive primaries the bronchogenic spread usually regresses during this time but the cavity may be persistent. Often in these cases we use prolonged therapy for months or even years with biweekly streptomycin and daily PAS until resection of the persistent cavity can be done with relative safety.

Dr. James B. Snow, Oklahoma City: Do you advocate streptokinase as an adjunct to the treatment of the meningitis?

Chairman Lincoln: We have tried this in a few cases and I would say the answer is no. We have seen severe reactions which are not easily controlled in the older children and the young adults may develop psychoses. I think that streptokinase has its place in tuberculosis, perhaps in bronchial lesions and in secondary abscesses. I think we are never going to be able to cure a high percentage of cases of tuberculous meningitis who are first seen in a late stage. There is not any doubt that a few have been cured but in the majority of cases, if you don't get them early you lose a large per cent of the cases. Of course, we keep on trying but I think we might do better to start on a campaign of trying to teach early diagnosis and increase our percentage of cures by diagnosing more cases in the first stage of meningitis.

Dr. Samuel S. Brown, Brooklyn, N.Y.: Would you please define progressive primary tuberculosis?

Chairman Lincoln: I mean locally progressive primary tuberculosis—a primary that, instead of disappearing slowly over a period of months leaving eventually only a small calcification, enlarges during the early months, develops a highlight on x-ray and evidences of bronchogenic spread from the cavity. If you follow these cases from the beginning you can often see the whole picture.

Dr. C. Read Boles, Clayton, Mo.: Would you discuss the diagnosis of tuberculosis in children who have received BCG?

Chairman Lincoln: If you don't have a positive tuberculin after BCG then I think the diagnosis is the same as if the child had not received BCG. When BCG has been followed by a positive tuberculin which has persisted, diagnosis is often difficult. That is Dr. Myers' objection to the use of BCG. I would like to hear what Dr. Levine thinks about it.

Dr. Levine: If BCG inoculation is successful in causing a tissue sensitivity to tuberculin, as evidenced by a positive tuberculin test, then it is rare to get primary tuberculosis pulmonary infiltration —because the primary focus has already been localized at the point of BCG inoculation, whether it is on the arm or leg.

In cases where the allergy following BCG vaccination disappears, there is again the possibility of a new primary tuberculous infection in the lungs. However, the occurrence of primary lesions of tuberculosis after a successful BCG inoculation is extremely rare.

Chairman Lincoln: Of course, Dr. Wallgren's idea is that BCG is a temporary help and should give you enough immunity so that the natural infection when it occurs will not be a progressive one.

Dr. Levine: Vaccination with BCG may be of some real importance in late adolescence and young adult life, for there is some reason to feel that during these age periods the primary pulmonary infiltration becomes progressive instead of subsiding and calcifying at the point of primary focus. Recently a study was made of soldiers in the Swedish Army which demonstrated that only a few months after having negative chest x-rays and negative tuberculin tests, a fair number had developed caseous tuberculous pulmonary lesions with cavitation.

In other words, there had developed a progressive primary rather than the usual sequence of a primary focus to calcification. If we can prevent a pulmonary primary in an adolescent or young adult by placing a primary lesion in the arm or thigh, we might possibly prevent the occurrence of such progressive primaries.

Dr. Thomas P. Saltiel, Chicago: Do you use streptomycin in early tuberculosis of the hip?

Chairman Lincoln: I think that would be one of its elective uses. We have used streptomycin when a child came in with acute tuberculosis of the spine with high fever for which no other cause could be found except tuberculosis. The child went on to eventual operation. He did not develop meningitis. We treat a good deal of bone and joint tuberculosis incidentally in our meningitis cases and most of them go on to progressive disease and surgery. There are, however, physicians who think that bone and joint tuberculosis responds to streptomycin. Cases have to be followed for a long time after treatment to be sure of permanent results.

Dr. Levine: Recently there was a paper in which it was stated that the test for bacterial resistance

to streptomycin is not comparable to the body reaction to streptomycin. In other words, by test, the organism may be quite resistant to streptomycin but it was felt that in the body streptomycin could still be effective.

Chairman Lincoln: I think there is no doubt about the fact that you can have a certain degree of resistance to streptomycin as found in the bacteriologic laboratory and still get benefits from streptomycin. We are quite sure of that in some cases. I am also sure that organisms from one portion of the body may be resistant and tubercle bacilli from another area may be sensitive to streptomycin. We had a child with endobronchial tuberculosis and meningitis and treated him with streptomycin and promizole® in the usual way. He was cured so the organisms in his spinal fluid probably weren't resistant. In a bronchoscopic examination about a year later we obtained a culture of tubercle bacilli that was completely resistant.

Question: How often do you have them return for spinal punctures after discharge?

Chairman Lincoln: We do punctures every week or twice a week, for at least 2 months after streptomycin is discontinued and if the child has a good home we let the child go home at the end of that period and come back every 2 weeks for a puncture; after a few months we try to secure a monthly tap for a variable time, never longer than a year.

Question: You mean you do have symptoms?

Chairman Lincoln: Yes, because while we have never had a relapse later than 43 days, we want to be sure.

Question: What tuberculin test do you think is the most suitable?

Chairman Lincoln: I think the best is a Mantoux test with PPD or Old Tuberculin. I use the patch test, too, as I have mentioned before. One important point in regard to the patch is to notice the date of the box; if it isn't too old, it is an accurate test if you are sure you know how to read a positive patch test.

Dr. Sidney R. Kaliski, San Antonio: Have you ever used patch tests quantitatively in the sense that you are using a time element of application for evaluating the degree of sensitivity?

Chairman Lincoln: No, and as you know the degree of reaction in any tuberculin test is not thought to be of value in prognosis.

Question: Do you use neomycin?

Chairman Lincoln: No, it is much too toxic.

Dr. Levine: The cases we studied were very different from those observed by Dr. Lincoln. Our observations were on children in tuberculous homes usually from the moment they were born. They received roentgenograms and tuberculin tests at approximately 3 month intervals, so we were in many cases actually able to see what is usually missed, the earliest onset of a primary tuberculous infection of the lungs, and follow through either until calcification or death.

Of the 90 children followed through the primary complex of tuberculosis, 27 acquired their infection during the first year of life, the remainder at a later period when they were able to walk. Of the 60 children who were ambulatory throughout the full course of the primary complex, except during the early febrile period, there were only 4 deaths. These children were in no way restricted—even attending school.

The tuberculosis mortality in these cases was derived almost entirely from the group of children under 2 years of age. It appeared that the age of the child at the time of infection rather than the method of treatment was the important factor in determining prognosis. There was no evidence that rest in bed influenced in any way the course of the primary complex or reduced the incidence of complications and no evidence that lack of rest in bed was in any way detrimental.

Dr. J. Arthur Myers of the Lymanhurst Clinic in Minneapolis, who has followed many thousands of tuberculous children, has stated that, in his opinion, a primary tuberculous infection will follow its own course whether a child rests in bed, has collapse therapy, whether they are as unrestricted in activity as normal children. Myers also minimizes the importance of the sedimentation rate.

We do not treat primary tuberculosis with streptomycin unless complications develop. We have not seen any real evidence that the primary pulmonary infiltration is influenced by streptomycin.

As a matter of fact, we have seen cases where a miliary tuberculosis, treated by streptomycin, clears completely on x-ray, leaving the primary infiltration exactly as it was before the hematogenous spread developed.

Question: You don't treat them in bed then?

Dr. Levine: Not at all, we let them go to school. Dr. Wallgren actually published a paper on this. He keeps his children in bed until the sedimentation time has gone to normal. We don't pay any attention to sedimentation time. In other words, he keeps some children in bed most of a year and then for the year following puts them in bed for perhaps 3 hours a day so they get some rest in the middle of the day. I can't help but feel there is some difference among the children that he treats in Europe.

Chairman Lincoln: Dr. Levine has brought out the important part of this controversy about the treatment of primary tuberculosis. I think we all agree that primary tuberculosis is potentially a serious disease; that it varies in different localities, possibly according to the degree of infection and according to a number of other factors about which we know very little; that it is the business of the pediatrician to follow his cases and to watch for complications. Dr. Myers has done a wonderful piece of work as far as antituberculosis work has been concerned but, unfortunately, he emphasized too much the fact that in his own group the mortality was low, and concluded from that, therefore, that tuberculous children needed no treatment at all. He implied that even supervision was not necessary and I think that did a great deal of harm because it influenced pediatricians to believe that it wasn't necessary to follow children who had acquired first infection tuberculosis.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

"A forum where discussion could be free, intelligent and continuous."

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

At the annual meeting of the State Chairmen of the American Academy of Pediatrics in 1952, Dr. Edward A. Wishropp made a brief report of the plan for giving comprehensive pediatric care in Windsor, Ontario. This had been studied by the Academy's Committee on Medical Care Plans.

In order that the membership of the Academy might have more information about the work of this important committee, the editor of this column requested Dr. Wishropp and Dr. Edgar E. Martmer to prepare a communication on this subject.

INSURANCE PLAN REPORT

THERE are many programs throughout the United States, Canada and several foreign countries, providing some degree of medical services for infants and children. These range from governmentally financed programs, offering supposedly complete care, to those furnished by individual pediatricians having agreements between the pediatrist and the parents.

Because no comprehensive review of these various plans has been made, the Executive Board of the American Academy of Pediatrics created a committee to study insurance plans and programs.

The president, Dr. Warren Quillian, appointed a Committee on Medical Care Plans as a fact-finding group. Serving with Dr. Edward A. Wishropp, chairman, are:

Region I—Dr. Harry L. Mueller, Winchester, Mass.
Region II—Dr. Fred Bush, Rochester, N.Y.
Region III—Dr. Kenneth Blanchard, East Orange, N.J.
Region IV—Dr. Luther Holloway, Jacksonville, Fla.
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Region VI—Dr. M. G. Peterman, Milwaukee, Wis.
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Region VIII—Dr. Ezra S. Fish, Beverly Hills, Calif.
Dr. E. H. Christopherson, Executive Secretary, ex officio

Some basic considerations, presented by Dr. S. J. Axelrod, Assistant Professor of Public Health at the University of Michigan, can be outlined as follows and these must serve as a working nucleus in determining a worth while and workable plan.

1. Administration
   a. Relation to Blue Cross, Blue Shield, other prepayment plans
   b. Independent sponsorship
2. Eligibility
   a. Dependents of subscribers already enrolled in Blue Shield Plan or children alone
   b. Age limit: under 1 year or pre-school or all children under 15 years of age
   c. Family income limits
3. Services to be Offered
   a. Limited: well-baby care, including routine immunizations, feeding advice, counseling on physical and emotional growth, or
   b. Comprehensive: above *plus* periodic physical examinations, treatment for illness in office, home, hospital; consultation on referral from general practitioner
4. How Are Services to be Provided
   a. Individual practitioners
      (1) General practitioners and/or pediatricians
      (2) Who is a "pediatrician"?
         (a) Diplomate of American Board
         (b) American Academy of Pediatrics "Survey" definition
   b. Group practice
   c. Hospital out-patient clinics
   d. Health Department services
   e. Visiting Nurse services
5. Payment for Services
   a. Fee-for-service
      (1) Establishment of fee-schedule
         (a) Office care
            i. Well-baby care including routine immunization
            ii. Periodic physical examination
            iii. Diagnosis and treatment of illness
         (b) Home care
            i. Night calls
         (c) Hospital Care
            i. Flat fee
            ii. Per diem charge
         (d) Consultation
   b. Capitation
   c. Combined fee-for-service and capitation
   d. Differential fees for general practitioner and pediatrician

6. Utilization of Services
   a. American Academy of Pediatrics Survey
      (1) General practitioners take care of 75% of all children; pediatricians, 11%; other specialists, 14%
      (2) On average day of practice of general practitioner, 9% of his patients' visits are for health supervision of well child; 21%, for sick child
      (3) On average day of practice of pediatrician, 54% of his patients' visits are for health supervision; 43%, for sick child; 3% for patients over 15 years of age.
   b. Trinity Hospital Plan, Little Rock, Arkansas, 1941
      (1) Group practice; comprehensive pediatric care
      (2) Office and home visits per subscriber per year

Age Group	All	Male	Female
Infants born during year	3.4	3.8	2.9
Under 5	4.3	4.5	4.0
5-9	5.0	5.3	4.4
10-14	3.9	4.5	3.5

   c. Health Insurance Plan of Greater New York, 1948
      (1) Group practice; comprehensive pediatric care
      (2) 57% of all services rendered by general practitioners; 8% by pediatricians; 35% by all other specialists;
      (3) Office and home visits per subscriber per year

Age Group	All	Male	Female
Under one year	13.1	13.4	12.8
1-2	4.9	5.2	4.7
2-4	4.7	5.0	4.4
5-9	4.7	5.0	4.4
10-14	3.1	3.5	2.8

   d. Windsor Medical Services, 1950
      (1) Individual practice; fee-for-service; comprehensive pediatric care
      (2) Office and home visits per subscriber per year

Age Group	All	Male	Female
Under 10	4.1	4.5	3.6
10-19	2.4	1.9	2.8

7. Standards of Care

From the above it is readily seen that very little information is available to cover insurance costs on an actuarial basis when pediatric care is considered per se. It is more or less a plan of budgeting expected expenses over a period of years. That is, it falls in the same category as does the obstetrical care now in effect in the Blue Shield plan in Michigan, which plan now pays for the delivery only and does not include prenatal or postnatal care. Therefore, it must be set up on a fee basis of expected expenses. Pediatric care is a surety and not an incident, the same as illness or accident. It means the spending of money of older members of the family or families without

children, to pay for the cost of prophylactic care of children. To this must be added the cost of recording and billing of such items. The Blue Shield has estimated such costs of accounting would be in the neighborhood of from 5% to 9%, depending on the extent of the enrollment.

In Australia there exists a governmental plan, wherein the individual family carries insurance, the costs distributed as follows: 45% paid by the government, 45% paid by the insurance plan and 10% paid by the individual, BUT, if no insurance is carried by the individual then all the fee is paid by the individual.

In discussing the Windsor plan with members of the Academy who reside in Windsor, Ontario, the following facts were brought out:

1. The insurance rates are about $7 per month for a family of three or more children. In addition there is a fee for the Blue Cross in order that hospital care can be included.
2. The fee for office visits allowed is $3 for pediatrician, $2 for general practitioner.
3. Consultation fee allowed is $5, the same as for initial office visits for pediatrician and $4 for the general practitioner.
4. Bills are sent directly to the Medical Service Plan and a special card is filed with information in code.
5. The plan is open only to those in the income bracket of $6500 annually, which, in Windsor, covers 95% of the population.
6. Medication is NOT paid for by the plan.
7. Well baby visits are limited to 5-6 per year.
8. Immunizations fees are limited to $1 per innoculation.

There have been complaints among general practitioners that pediatricians should not receive more than they for doing the same work and that pediatricians should confine themselves to consultation work only. Also hospitals have been compelled to set up a registry of surgery to control elective operations. That is, some men in the profession have abused the privilege of operating on chronic appendices, etc. An attempt has been made to decline fees for non-essential operations.

There seems to be an inclination for the public to tend to seek pediatric service by specialists rather than general practitioners because they actually do prophylactic care and examine the patient thoroughly.

EDWARD A. WISHROPP, M.D., *Chairman, Grosse Point Farms, Mich.*
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TRENDS

By John P. Hubbard, M.D., *Contributing Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

THE CHILDREN'S BUREAU ANNUAL REPORT

THE report of the Children's Bureau contained in the Annual Report of the Federal Security Agency* is a useful summary of the Bureau's appraisal of some of the gains that have been made during the course of the year and the needs yet to be met for the Nation's children. It also includes a review of the Bureau's resources and planning for the further development of the health and welfare of children. The following are excerpts taken directly from this report. Those interested in a fuller description of the Bureau's activities, especially the programs which are primarily of a welfare nature, will wish to consult the report itself.

Our Nation's Children

In 1949, one-half the children of the United States lived in families with incomes of less than $3,080 a year. One-fourth were in families with incomes under $2,000. The families of the 3 million children living with only 1 parent had an average income of $1,597, half the average income of the families of the 39 million children living with both parents ($3,174).

About 1 million children—truly the Nation's disadvantaged children—are in families of the migrant agricultural workers.

In 1950, 1 out of 5 mothers with children under 18 years of age—4.6 million mothers—worked outside the home. Of these mothers, 1.7 million had children under 6 years. About 6 million children under 18 years were in homes in which both parents worked. The mothers of one-sixth of all children living with both parents were employed; the mothers of half the children in broken families were at work.

Maternal deaths were 7.2 per 10,000 live births in 1950 (provisional), a reduction of 79 percent since 1940. Despite this improvement, the mortality rate of Negro, Indian, and other nonwhite mothers (18.4) continued to be more than 3 times that of white mothers (5.5). Infant deaths per 1,000 live births dropped from 47.0 in 1940 to 29.2 (provisional) in 1950—a cut of 38 percent. Of all deaths under 1 year in 1949, more than half were due to causes peculiar to early infancy, and of these deaths approximately two-thirds were associated with premature birth.

Childhood deaths have also been reduced sharply. The 1949 rate of 9.2 deaths per 10,000 children aged 1-14 years represents a decrease of 41 percent since 1940, when the rate was 15.5.

The Bureau at Work

Funds available to the Children's Bureau in 1951 for its activities, excluding international cooperation financed by the Department of State and the special expenses connected

* Annual Report of the Federal Security Agency, Social Security Administration, 1951, Washington, D.C., Superintendent of Documents, U. S. Government Printing Office, pp. 48-64.

with the Midcentury Conference, were $1.5 million for its own activities and $30,250,000 for grants to States under the Social Security Act.

Special emphasis during the year was placed on (1) the Midcentury Conference; (2) laying the foundation, through cooperative planning with the States and with representatives of voluntary agencies, for the expanded programs made possible by increased grants authorized by the 1950 amendments to the Social Security Act; (3) improving, through Bureau-wide planning, the quality of service given by the staff; (4) assessing the impact on children and young people of mobilization and preparations for defense; and (5) extending international cooperation activities.

Increasing Knowledge and Disseminating Information

The Bureau resources for basic research, carried on under the act of 1912, are limited, but the Bureau serves as a center of information about research under way throughout the country; participates in a few selected research undertakings of strategic importance; points up, with the aid of experts in various fields, the areas in which research is most needed; and interprets the results of research to parents and others concerned with children.

Supplements to the Bureau's bulletin, Current Research in Child Life, reported 803 new studies under way. Fully one-third of these are concerned with physical health and disease, and about one-fourth are in the field of psychology. Many of the social service studies reported are of the survey type.

The Bureau in cooperation with Fisk University launched a research project to study cultural differences in child rearing. Plans for a similar study, which will make regional comparisons possible, were initiated with the Institute of Child Welfare at the University of Minnesota. The Bureau reviewed materials on retrolental fibroplasia and accidental suffocation of infants as a basis for encouraging research in these fields. A plan to evaluate the relation of mortality of premature infants to special hospital facilities for their care was developed, and a pilot study was started with the Maryland Department of Health to test the plan.

A system for uniform tabulation of births and deaths resulting from prematurity, developed by the Public Health Conference on Records and Statistics with the aid of the Bureau and the Public Health Service, was put in operation by the State health agencies.

Cooperation with States

The 1950 amendments to the Social Security Act authorized $37 million for the fiscal year 1951 for grants to the States for child health and welfare programs. Because the amendments came into effect after the first quarter of the fiscal year, only $30,250,000 was appropriated: $13,200,000 for maternal and child health services; $9,975,000 for crippled children's services; and $7,075,000 for child welfare services. All States, the District of Columbia, Alaska, Hawaii, Puerto Rico, and the Virgin Islands shared in these grants. Federal participation in the program of the Arizona crippled children's agency was suspended throughout the fiscal year because of failure to reach an agreement on extending treatment services to Indian children.

Statistics on volume of health services relate to the calendar year 1950 and reflect only slightly the expansion made possible by the Social Security Act amendments.

Services for mothers and children under the State maternal and child health programs continued their upward trend. These services are aimed primarily at providing health supervision—with a limited amount of medical and dental treatment—to expectant mothers, infants, and preschool and school children. State reports on medical services show that 171,000 mothers attended prenatal clinics, an increase of 3,000 over the 1949 total; more than 59,000 women were given postpartum medical examinations, an increase of 6 percent; and more than 258,000 expectant mothers received nursing service, an increase of 7 percent. Infants and preschool children attending medical conferences increased 4 percent, to 723,000, but there was a decline of 3 percent, to 1,100,000, in the number receiving public health nursing service. On the other hand, nursing visits in behalf of school children increased 8 percent to a total of 2,894,000.

Preliminary estimates on crippled children served in 1950, based on reports from 46 States, showed that approximately 215,000 children received physicians' and related services during the year, or 35,000 more than were so served in 1949, an increase of 18 percent. Some two-fifths of these children were new to the program. The types of service they received include clinic service, hospital in-patient care, convalescent home care, and physicians' home and office visits. Some 40,000 children received hospital in-patient care, slightly more than in the preceding peak year of 1949. Care in hospitals was provided for 1,450,000 days, and the average length of stay per child was about 36 days. More than 5,000 children, slightly fewer than in 1949, received care in convalescent homes for an average of about 94 days each.

Several States have set up or improved special hospital centers to provide better care for premature infants and to have suitable training centers available for physicians and nurses. The use of fluorides to help prevent dental decay received great impetus in maternal and child health programs. Other programs that are expanding slowly are medical care for complicated obstetrical cases, pediatric clinics, and pediatric and obstetric consultation services. Considerable interest in school health programs is developing. Preliminary reports of a demonstration school health program in Washington County, Md., based on screening by teachers and nurses and careful diagnostic and corrective services for children found to need such service, and carried on in cooperation with medical groups and hospitals, indicate great potentialities for influencing school health practices throughout the country. A staff conference held by the Children's Bureau, the Office of Education, and the Public Health Service resulted in a statement on recommended practices and priorities for health services for children of school age.

A number of States increased appropriations for their crippled children's programs by 10 to 30 percent; others made special appropriations for such programs as cerebral palsy and for hospital or convalescent facilities for crippled children. Several States broadened their definitions of a crippled child to include children with epilepsy, and began to develop diagnostic and treatment facilities for such children. An epilepsy demonstration program in Maryland, started at the beginning of the fiscal year, made rapid progress toward becoming a State-wide service. Services for children with cerebral palsy continued a major concern of State crippled children's agencies. Some States established additional cerebral palsy centers and clinics during the year.

In January an advisory committee including educators and State health personnel from various professional fields related to health services for mothers and children met

with the Bureau. The committee recommended that the Bureau, in considering the use of grant funds for training projects, give priority to the training of physicians in the public health aspects of maternal and child care and in the concepts of child development to prepare them for leadership as teachers and consultants. Among the training projects conducted this year with the aid of Federal funds were an institute on the public health aspects of rheumatic fever and heart disease in Connecticut, a joint training program for physicians and nurses on the care of premature infants in New York, and a cleft palate training program in Illinois. Plans for training programs in epilepsy in Illinois and Massachusetts were approved. Conferences were held with directors of courses for the graduate training of nutritionists and with staff of university schools of nursing on preparation for work in public health programs. An institute on medical-social practice was held for medical-social consultants from a number of States.

For All Children

In bringing together much of what we know about the development of health personality in children, the Midcentury White House Conference revealed the great gaps in our knowledge, and the need to verify through objective research much that we now assume to be true. Some of the areas in which additional research is needed are the fetal period of growth and the role of nutrition in this period; the relative importance of early and later stages of child development; ways in which children react to differences among children within their own age groups; the interrelation of organic needs, such as feeding, and emotional development; the functioning of the family in relation to economic practices—for example, the employment of mothers; child development in different cultures; the wastage of human life from high infant and maternal mortality which continues in many localities in the United States; and methods of measuring the effectiveness of child health and welfare programs.

The 1950 amendments to the Social Security Act authorized appropriations for the fiscal year 1952 and thereafter of $41.5 million annually—$16.5 million for maternal and child health services, $15 million for crippled children's services, and $10 million for child welfare services. Appropriation of the full amounts authorized is urgent to provide needed expansion of programs and to meet rising costs of service. Continued and increased emphasis should be placed on the relationship of these programs to those conducted under voluntary auspices and on the leadership of national voluntary organizations in developing both public and private programs.

Because of the great opportunities for improving the health of school-age children through the combined efforts of the schools and the health agencies, additional Federal aid is needed to expand health programs for these children. Emphasis in school health work should be shifted from mass medical and dental examinations to more constructive methods of screening out the children who have health problems and assuring for them adequate medical diagnosis and treatment.

Professional training for all personnel who will serve children—physicians, dentists, nurses, teachers, nutritionists, psychologists, social workers, and recreation leaders—should include a common core of knowledge of the development of personality in children. Expansion of training programs in the child health field is urgent, and priority should be given to training physicians in the public health aspects of maternal and child care and in the growth and development of children.

For Children and Families Under Special Handicaps or Tensions

If a fairly high level of mobilization for the Armed Forces is to be maintained, a program somewhat similar to the emergency maternity and infant care program for wives and infants of enlisted men, carried on by the Children's Bureau during World War II, will be needed. The statement of principles to be considered in proposals for such a program, which was developed by the Bureau in consultation with medical, hospital, and other groups, affords a basis for legislation in conformity with the lessons learned from World War II experience and developments since that time.

Planning for services for children of employed mothers should build on experience during and since World War II and develop a broader range of services than has hitherto been available. In recognition of the contributions mothers make in the home and their responsibilities for children, organized recruitment of mothers by industry should be deferred until full use has been made of all other sources of labor supply. However, the right of mothers to make their own decisions as to employment should be respected and community measures should be developed through the schools and community welfare and health agencies to provide suitable care for their children. Because of the impact of defense production on the employment of mothers, Federal aid for planning and providing day care services for their children is needed not only in areas where the defense program has greatly increased the population but also in other areas where substantial numbers of mothers are employed.

The needs of children in low-income families and the possible effects of low income on personality development in children should be kept constantly in mind in the development of economic and social policies.

There is need for expanding the social services of public and voluntary welfare agencies for children living in broken homes and for relating the services more closely to those of other agencies, such as the courts that deal with nonsupport, separation, divorce, and guardianship.

Federal agencies in cooperation with State and other agencies should take concerted action to develop effective services for the children of agricultural migrants, who are among the neediest groups in the population.

Particular attention should be given to meeting the social and emotional as well as the physical needs of handicapped children. Institutional care and community services for retarded children should receive special consideration.

Every effort should be directed toward developing more nearly adequate community services for emotionally disturbed children through the cooperation of health, child guidance, educational, and social agencies. There is need for more emphasis on providing treatment in psychiatric clinics for children, and more effective methods of selecting children who need intensive treatment, and on developing adequate resources for nonresidential treatment. Increased resources for training all personnel who deal with disturbed children are essential.

The apparent increase in the number of young persons addicted to the use of narcotics calls for a comprehensive program of tight control of supplies, apprehension of traffickers, treatment and rehabilitation services to meet the medical, social, and psychological needs of young addicts, and community education.

The Gist of Things to Be Done

The realization of our goals for children requires a clear recognition of the importance of doing everything possible, primarily through the family, the school, the church, and other agencies of the community, to assure their happiness and a good start on life's journey. Children are always an emergency, and meeting their needs cannot be postponed because of the necessity for mobilizing for defense. We should be able, within the coming decade, to bring maternal and infant mortality down sharply, especially among those groups and in those areas where the rates are still very high. We should be able to develop the resources, the organization, and the trained personnel necessary to provide avenues for the application of scientific knowledge to the rearing of children in every community in the land. We should be able to expand greatly research in those aspects of child life and development concerning which additional knowledge is urgently needed. Above all, we need to recognize that the basic ingredients of the growth of healthy personality are the faith, hope, and love of those responsible for the child's nurture within and outside the home, and their regard for each child's innate dignity and worth.

NEWS AND ANNOUNCEMENTS

Dr. Clifford Sweet, for 30 years chief of staff of Children's Hospital of the East Bay in Oakland, Calif., was honored by the medical staff there on May 21, 22 and 23, with the inauguration of the "Clifford Sweet Clinics and Lectureship."

The event opened ceremonially with the unveiling of a new portrait of Dr. Sweet by Spencer Macky, president of the California College of Arts and Crafts in Oakland. There followed a 3 day schedule of clinical conferences, with a public lecture on May 23 by Dr. Irvine McQuarrie, professor and head of the department of pediatrics, University of Minnesota. The Sweet Clinics and Lectureship will be an annual event.

* * *

The following diplomates have been certified by the American Board of Pediatrics, Inc.:
New York City—Feb. 1, 2 and 3, 1942

Alperin, Leonard Jack, 10640 Carnegie Ave., Cleveland
Baehren, Paul F., USAF Hospital, Wright-Patterson AFB, Dayton, Ohio
Bashe, Winslow Jerome, Jr., Children's Hospital, 1740 Bainbridge St., Philadelphia
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Blackmore, Betsy Snyder, 1305 Neil Ave., Columbus, Ohio
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Botstein, Anne, 3215 Netherland Ave., New York City
Calcagno, Philip Louis, 219 Bryant St., Buffalo, N.Y.
Cartland, John E., Jr., 85 Jefferson St., Hartford, Conn.
Cheung, Mung Wah, Children's Med. Service, Bellevue Med. Center, 477 First Ave., New York City
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* * *

Dr. Rockwell M. Kempton of Saginaw, Mich., died on April 5, 1952. He was a fellow of the American Academy of Pediatrics.

BOOK REVIEWS

TREATMENT OF ASTHMA, SOMATIC AND PSYCHIATRIC, edited by Harold A. Abramson, M.D., Baltimore, The Williams & Wilkins Company, 1951, $11.00, 751 pp.

Dr. Abramson is Chief of the Allergy Clinic at Mt. Sinai Hospital of New York and Assistant Professor of Physiology at the College of Physicians and Surgeons. His purpose in organizing this book was to coordinate knowledge of the allergic nature of asthma in the child and the adult, with certain methods of therapy connected with its psychogenic aspects. He feels there has been a lack of mutual understanding and even awareness of each other's problems, between allergists and psychiatrists, in dealing with asthmatic patients. To combat this situation, he has assembled a group of authors who have contributed chapters dealing with their fields of special interest relating to asthma. He himself has chapters on the physiology of respiration, on psychotherapy of respiration, and on psychotherapy of asthma. Other contributors include: Hansel, Miller, Peshkin, Ratner, Wittich, Forman, Rogers and Colfer. There is little coordination of the various chapters or of the 5 general headings under which they are grouped. As a result, any gap existing between allergist and psychiatrist does not appear to have been closed to any great extent. Abramson believes pure psychogenic asthma is rare or nonexistent, but also feels that in all except special situations the asthmatic patient cannot be treated properly by a scrutiny only of his immunologic state. While this book will contain chapters of interest to those dealing with asthma, it may not persuade them appreciably for or against acceptance of these concepts of the author.

KYMOGRAPHISCHE ROENTGENDIAGNOSTIK ZUR BEURTEILUNG DES HERZENS IN BEISPIELEN (Roentgenkymography in Diagnosis of Heart Disease: Presentation of Clinical Cases), Prof. Dr. P. Stumpf, Stuttgart, G. Thieme, 1951, D.M. 25.50, 120 pp. with 164 illustrations.

As written in the Foreword by the author, the monograph can be considered the beginning of a comprehensive book on the value of roentgenkymography. The book shall be a further development of the work *Bewegungslehre innerer Organe* published in 1936 by Stumpf, Weber and Weltz. An experience of 25 years gives to the author the possibility to lend to the practitioner the outlines of the method and some useful advice for the daily routine work.

As a matter of fact, whereas roentgenkymographic technic is well described in almost every book of roentgenology, typical patterns in the various pathologic conditions are not systematically considered.

Avoiding any discussion about several modifications subsequently made of the original method, the author presents only personal observations, following a standard technic, i.e., mobile grid with multiple slits 12 mm. apart, focus-film distance of 1 meter, exposure time of 2.4 seconds, load 80 kV and 40 to 50 mA.

In the first part of the book the general criteria of roentgenkymography are stressed. Two different movements interfere in the production of the kymographic waves: volume changes (filling and emptying of the chambers) and pendular movements of the heart. Combination of these movements can sometimes result in a kind of compensation, so that no apparent wave is seen. In this case, variations of the density of the examined border take place, which are indicative of volume changes.

In the second part, the typical kymographic patterns are drawn from the discussion of 40 clinical cases. When needed, clinical and electrocardiographic data are presented too. In some cases exertion-test was performed, and the results, consisting of change of the cardiac rate and of the shape of the ventricular waves, are discussed.

Kymographic characteristics of mitral insufficiency (prominence of the pulmonary conus with dicrotic waves) and stenosis, aortic insufficiency (great amplitude of the waves and lateral plateau at the left ventricular border) and stenosis, and combined valvular defects, are described.

A case of congenital mitral stenosis and a case of complex malformation are presented. Interesting cases are those of apical infarction, with systolic expansion of the damaged wall; muscular insufficiency from muscular dystrophy; cardiac neurosis (after exertion); auricular flutter; hypertension (dicrotic aortic wave) and aortic sclerosis (absence of aortic pulsations).

Differential diagnosis between aortic aneurysm and mediastinal tumor is emphasized.

Tables for calculating the cardiac rate on the roentgenkymogram and for the evaluation of the cardiac diameters are added at the end of the book.

The illustrations are very clear and significant in every case, although somewhat reduced in size. In several cases, enlarged particulars of the kymograms give supplementary evidence of the most typical patterns.

The edition is accurate.

ZAHNÄRZTLICHE PROBLEME IN DER KINDERHEILKUNDE (Problems of Dentistry in Pediatrics), F. Parabo, Basel, Benno Schwabe, 1951, Fr. 14.50, 120 pp., 121 illustrations.

F. Parabo, who is pediatrician as well as dentist, has selected his material from the daily contact with the residents over a period of 5 years. E. Fanconi emphasizes in his foreword how this continuous cooperation prevents the divergent views when a pediatrician reassures the parents their child is too young for the correction of a malocclusion, whereas the dentist explains some time later it would then be too late.

Discussion of such controversial problems as thumb-sucking and orthodontic anomalies at the bedside in daily routine is an important result of this book. But still more important questions of mutual interest for the pediatrician and dentist as difficult eruption, caries, toxic gingivitis, after-treatment of extraction are considered from the metabolic, nutritional, hormonal and pharmacologic viewpoint.

Technical terms of dentistry are omitted, the text is simple and concise, and the illustrations with brief legends (more pictures than pages) are so excellent that one learns without the uneasy feeling of being forced into a new pediatric subspecialty.

The main chapters discuss: developmental disorders, dental diseases, inflammations of the oral mucous membranes, tumors, dental surgery, fractures and dislocations, and types of malocclusion.

PUBLIC HEALTH NURSE AND HER PATIENT, Ruth Gilbert, ed. 2, Cambridge, Mass., Harvard University Press, 1951, $3.75, 348 pp.

Designed particularly for public health nurses, but of value to all nurses, is Miss Gilbert's new edition of *The Public Health Nurse and Her Patient*. This edition deals first with health teaching, relationships and attitudes, and prepares the reader for the chapter on "Nursing the Sick Patient." Newer concepts of mental health are emphasized without the use of technical terms and focused through the use of excellent case material. Miss Gilbert has a background of training in both psychiatric social work and nursing and with long experience in teaching. She helps nurses to understand more about their own motivations and reactions to individuals, which help or hinder the progress of their patients toward recovery. As the nurse understands racial and cultural patterns that influence families in accepting health teaching, she avoids making many superficial judgments. The chapter on relationships with co-workers and the emotional factors in the use of authority is helpful for the administration of any profession.

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